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THE NERVOUS AFFECTIONS OF THE HEART.*

FRIEDRICH MÜLLER, M.D.

MUNICH, GERMANY.

The Harvey Society has been founded for the purpose of forming a connecting link between the scientific research work of the laboratories and medical practice. I am greatly indebted to your president for his kind invitation to deliver a lecture before your society.

It is my intention to address you to-night on the nervous diseases of the heart. It may be asked whether this is a problem sufficiently scientific to conform fully with the purpose of this society. I hope it is. As a professor of clinical medicine I hold the opinion that an observation made at the bedside is as well to be considered scientific as an observation made on an animal; nor do I think that, because it is unable to speak, the rabbit is a more scientific animal than man.

I have selected this subject because it illustrates better than many others that our clinical conceptions are founded on experimental physiology. It is not long since we first ventured, and then only with some hesitation, to apply conclusions drawn from laboratory experiments to the pathology of the human heart. Now, since Deneke's successful experiments on the human heart, we see our analogies in a clearer light. Deneke isolated the heart of a criminal immediately after execution, and by perfusing it with Ringer's solution and then with blood, found that it beat regularly for a considerable length of time and obeyed the same general laws that apply to the heart of the dog and rabbit.

Before we can comprehend the nervous *pathology* of the heart, we have to ask what rôle the nervous system plays in the *normal* movements, not only of the heart, but of the blood vessels as well, for we must realize at the start that we can never look on the heart as a separate entity, but that the heart of the higher as well as of the lower animals is only a part of the whole circulatory system, and that it stands in closest relationship with the blood vessels.

We know now that the heart removed from the thorax and cut off from all its connections with the cerebrospinal and the sympathetic nervous system pulsates regularly. Therefore, we draw the conclusion that the nerves running to the heart never originate the heart movements,

* Harvey Lecture, delivered at the New York Academy of Medicine, March 9, 1907.

although they may influence them, interfere with, and even stop them. The origin of the pulsations lies in the heart itself and it is the flow of the blood through the heart, and especially through its own arteries, which not only acts as a nutrient, but also affords the stimulus. The same stimulus can be produced also by Ringer's solution, and Howell of Baltimore has proved that the calcium ions especially are of importance.

To this *constant* stimulus the heart answers with *rhythmic* contractions quite in the same manner as the stomach, the intestines and the ureters respond with rhythmic peristalsis to the constant stimulus of their contents. The stimulus acts on the muscle of the heart, but it is not yet clear whether it is on the muscle fiber itself that the stimulus first acts, or whether the fine network of intrinsic nerves takes up the stimulus and transfers the irritation to the muscle fibrils. While Engelmann and the Leipzig school adhere to the muscular hypothesis, Bethe and recently Hering strongly defend the nervous origin of the irritation.

The irritability of the heart muscle ceases during and immediately after the systolic contraction and returns gradually during the diastolic pause until it reaches a point sufficient to respond again with a new contraction to the continued stimulus of the blood flow.

This refractory period may be shortened, as is the case in paroxysmal tachycardia, or it may be of longer duration when the irritability of the heart muscle is impaired by pathologic processes.

Every part of the heart is irritable, and every part answers to the normal stimulus with its own rhythm, but the irritability is developed in the highest degree in the venous part of the right auricle, and this most easily excitable part, whose own pulsations are more frequent than those of the ventricles, takes the lead of the other parts and determines the rate of their pulsations. So the venous part of the auricle forces its rhythm on the other parts of the auricles and on the ventricles with which it is connected.

The impulse from the auricles to the ventricles goes through the bundle of His. We have learned its nature and course only within the last year, when Tawara published his studies on the heart of different animals. In the human heart the shape and distribution of the His bundle seems to be less simple than in dogs, sheep and calves, and is not yet fully known. In the lower animals His' bundle arises in the form of a knot in the septum auriculorum, passes immediately in front of the septum pellucidum to the muscular wall between the right and left ventricle, divides into two branches, either of which runs as a closed bundle to the apex of each ventricle and divides there into fine filaments supplying the papillary muscles and all the other parts of the ventricular

walls. This bundle consists of peculiar shaped muscle cells first described by Purkinje. The transmission of the impulse from the auricles to the ventricles occurs with a definite delay, and it seems that the peculiar construction of the Purkinje muscle gives an explanation for this delay.

Both ventricles act synchronously and, indeed, this exact synchronism remains intact for as long a time as the two ventricles are connected by their muscle bundles. Hering concludes from his experiments on animals that a separate contraction of a single ventricle never occurs, and that the old clinical conception of hemisystolia was erroneous. When we consider that the muscle bundles of the right ventricle overlap to a considerable extent the central muscle nucleus of the left ventricle, and are closely mingled with it, this view looks very reasonable. But Kraus and Nicolai, in their latest experiments, conclude from the electrocardiogram of the human heart that in some cases of irregularity a dissociation between the contraction of the right and left ventricle does take place.

When the conducting path between auricles and ventricles becomes impaired the delay between the auricular and ventricular contractions will be longer, or some of the ventricular contractions may fall out altogether, so that, as Erlanger has demonstrated, not every auricular contraction is followed by a ventricular one. Not only anatomic lesions of the His bundle, but also some poisons (digitalis) and nervous influences increase this delay and, therefore, are able to produce omissions of single ventricular contractions.

If the His bundle is completely cut across, the ventricles do not remain permanently at rest; after a short stop they again begin to pulsate, but in their own rhythm, which is totally independent of the auricular movements and is characterized by its slow rate—thirty to twelve beats per minute. This is the case in the Adams-Stokes symptom-complex of paroxysmal bradycardia, and this disease is, therefore, not to be considered as a nervous one. In a very marked case of paroxysmal bradycardia, which has been studied in my clinic, we found at the autopsy a large white scar on both sides of the septum ventriculorum exactly at the site of the His bundle; similar observations have been reported by others. It is not yet clear why in such cases of severe anatomic lesions and destructions of the His bundle a permanent dissociation and a constant bradycardia does not take place, and why in such cases periods of complete dissociation commonly alternate with periods of two, three or four auricular contractions to one ventricular contraction, and sometimes with periods of one to one, viz., those of normal type.

If any part of the heart muscle is struck by an extra stimulus in

addition to the normal one, it can respond with an extra contraction or a premature systole, which interferes with the normal rhythm. The extra systoles are, according to our observations, commonly of a shorter duration, and they are of lesser intensity the sooner they follow after the end of the preceding normal contraction. The extra systolic contractions may start from the auricles or from either ventricle, and they are the commonest source of irregularity. In the human heart we observe these extrasystoles especially when the muscle has to struggle against an abnormal high blood pressure and against a condition of congestion, or when the heart muscle has become abnormally irritable. This is the case in many myocardial affections. We may say, therefore, that extrasystolic irregularities manifest themselves especially when the mechanical power of the heart is in disproportion to the opposing forces.

We have seen that the cardiac muscle is an automatic apparatus. Yet this apparatus works under the permanent control and influence of the central nervous system.

The nerves which run to the heart influence the frequency of contractions, their type and strength; they also increase or diminish the myocardial irritability and the transmission of the stimulus from one part to the other. We shall never be able to find our way through the inextricable network of nerve plexuses running to the heart and surrounding it, but we know something about the functions of the vagus and of the sympathetic nerves. The inhibitory influence of the vagus seems to be of greater importance than the augmentatory one of the sympathetic. The vagus nerve arises in that important region of the medulla oblongata where we find also the centers for respiratory movements and of the vasomotor system, and we are sure that these centers are in closest connection to each other.

The vagus sends fibers especially to the venous part of the auricles, and these particular fibers alone exert a chronotropic influence, that is, they affect the frequency of the heart contractions. Other parts of the vagus run to the septum auriculorum and ventriculorum and have an inhibitory action on the irritability and the energy of the muscular contractions, as well as on the conducting functions of the His bundle.

The vagus passes to the heart as white, medullated fibers. These do not end in the muscular fibers directly, like the motor nerves of the voluntary muscles, but seem to end exclusively in ganglionic cells, from whence non-medullated, gray fibers issue. The vagus is, therefore, to be considered merely as a preganglionic nerve, and we must realize that there is no essential difference between the vagus and the white rami communicantes of the spinal cord going to the sympathetic ganglia.

Both pass as white fibers from the central nervous system to sympathetic ganglion cells and both innervate involuntary movements.

Besides these centrifugal nerve bundles, the vagus has also a centripetal part, the so-called depressor nerve. This is not so much the sensory nerve of the heart itself as of the aorta, and it runs to the centers in the medulla oblongata. If the pressure in the aorta becomes too high, an impulse is carried through the depressor nerve to the vagus and vasomotor centers and produces an inhibitory reflex on the heart and a lowering of the blood pressure.

Summarizing, we can say the vagus reduces the work of the heart to that degree which is sufficient for the momentary exigencies of the circulation. The vagus is set in action by the heart itself or by the aorta whenever a protection for the heart is needed, and it is set in action by other organs, whenever a diminution of the blood supply is wanted.

On the other hand, the accelerans of the sympathetic system stimulates the heart to a greater effort and to a more frequent action for the benefit of other organs, for instance, of the working muscle. Every strong exertion of the voluntary muscles raises the frequency and the effort of the heart by way of the sympathetic nerves.

The sympathetic accelerator nerves leave the spinal cord at the level of the first of the fifth dorsal segment in the form of white, medullated, rami communicantes. They issue with the anterior roots and run to the ganglion stellatum and ganglion cervicale inferior. The postganglionic gray fibers arise from these ganglia and run to the various parts of the heart. Some of the sympathetic fibers pass to the venous parts of the auricles, and it is plausible to believe that these only have an increasing effect on the cardiac frequency. Other fibers of the sympathetic go to the ventricular muscle and increase the force of contraction, the irritability and conductivity, and shorten the duration of the systole.

It has been in doubt for a long time whether the sympathetic carries any centripetal, that is, sensory fibers. The embryologic origin of the sympathetic nerves and ganglia from the posterior spinal roots and the intervertebral ganglia seems to prove that there are indeed sensory functions in the sympathetic system, and many experimental and clinical observations also speak in favor of this belief. These sensory fibers of the sympathetic carry impulses of which we ordinarily are not conscious, and which are involved in the manifold unconscious sympathetic reflexes. The well-known fact that in angina pectoris a distinct pain is felt in the region of the lower cervical or the uppermost dorsal

spinal segments, and that often an area of hyperesthesia can be detected in parts of the arm and chest receiving their nerve supply from the same spinal segments (Head) leads to the conclusion that sensory fibers run from the heart to these segments of the spinal cord, for, as far as we know, there are no other paths for these sensory fibers except in the sympathetic system. Hence this clinical observation speaks in favor of the supposition of centripetal sympathetic fibers.

The double innervation of the heart through inhibitory and augmentatory nerves corresponds entirely to the innervation of all the other organs containing involuntary muscle, the stomach, the intestines (where we again see the vagus as an antagonist of the sympathetic), the bladder, but particularly the blood vessels. The blood vessels, and especially the finest arteries, are, like the heart, under the influence of inhibitory (dilatator) and augmentatory (constrictor) fibers. Indeed we can say that the accelerator (augmentatory) cardiac nerves are simply a part of the general vasoconstrictor sympathetic nervous system.

The vasoconstrictor nerves leave the spinal cord in the anterior roots in the form of white rami going to the sympathetic ganglia, from the dorsal to the third lumbar segments, the splanchnics belonging to these preganglionic white fibers. It will be remembered that the vasodilator nerves arise with the cerebral nerves, such as the vagus, and with the posterior roots of the spinal cord, from the uppermost cervical to the sacral segments.

Besides this central nervous influence on the caliber of the blood vessels we must suppose also certain local automatic contractions and dilatations of the finest arteries and capillaries which continue their action when all nerve supply has been cut off. The researches of Stricker and of others of recent times seem to prove that the automatic action of the capillaries plays an important part in the circulation of the blood and lymph. Be this as it may, it is certain that the vasomotor nerves have a very powerful influence on one of the most important and incomprehensible regulatory mechanisms, viz., the maintenance of the normal blood pressure, a regulatory mechanism whose importance stands in no respect below that of the maintenance of the body temperature.

This whole regulatory mechanism of the heart and vessels works under the control of the central nervous system, especially the brain; it responds to every incident in the life of the body, to psychic excitement, joy, fear and depression, to attentiveness, mood and fatigue; every muscular exertion, all changes of temperature act on it, and through it on the heart and vessels and blood pressure.

The morbid results of many cardiac diseases, of myodegenerations of

mitral or aortic stenosis, find a compensation in vasomotor contractions. On the other hand, we see that temporary or lasting changes in the blood vessels find a compensation through an increase or a diminution of the heart work.

Now that we have reviewed some general conceptions of the part played by the nervous system in the entire circulatory apparatus, let us consider in what form disturbances of the nervous system manifest themselves on the circulation.

Cardiac symptoms may sometimes arise from coarse anatomic lesions of the central nervous system or the vagus. Cases have been reported in which paroxysmal tachycardia was the consequence of a syphilitic disease of the basis cerebri and the oblongata, and severe compression of the vagus trunk is said to have provoked attacks of bradycardia and even of momentary stoppage of the cardiac beat, but it is not yet known whether we may regard some cases of the Adams-Stokes disease as a consequence of a damage done to the vagus or whether all such cases belong to alterations of the His bundle.

Far more frequently than with organic lesions of the nervous system do we see cardiac and vasomotor symptoms in connection with a general and *functional* nervous disease, especially with neurasthenia. In neurasthenia the irritable weakness and instability are not confined to the mind and the cerebral functions alone, but often involve a debility of the peripheral nerves also. Along with neurasthenia proper we must maintain with Möbius the old conception of nervousness. Nervousness is characterized by an over-irritability of the mind and the central nervous system. Irritation of one center irradiates farther and draws into play more centers than normally; therefore, all reflex functions are exaggerated. With nervous individuals disorders of the circulatory system play a very important part, and, indeed, a great many symptoms of neurasthenia and nervousness find an explanation in local or general disturbances of the heart and the vasomotor system.

Among the symptoms of the nervous heart we have first to consider *alterations in the rate of pulsations.* We note that usually the frequency of pulsations is increased and often to a high degree. But the increase is seldom a permanent one. A permanent acceleration points rather to other cardiac diseases. It is far more common, and very characteristic of nervous disturbances, to see periods of rapid pulse alternate with a normal rate or even with periods of bradycardia. Indeed the patient who has attracted our attention during the consultation because of his stormy, excited and frequent cardiac action, complains often less of the tachycardia than of the slow heart rate which he has observed in the

morning after sleep or during rest and which, if he anxiously palpates his pulse, gives him the hypochondriacal impression of cardiac weakness.

In short, the nervous heart reacts with an excessive alteration of frequency to all those conditions which produce in the healthy individual only a moderate increase of the pulse rate, for example, to the digestion of food, to coffee and alcoholic drinks (intolerance against alcohol) to every kind of muscular exertion, but above all to psychic impressions. It is characteristic that the increase in frequency is far more marked during psychic disturbances (as called forth, for instance, by fear of the doctor) than during muscular work. Muscular work provokes in the nervous heart an acceleration of the pulse rate, but not the symptoms of defective circulation or breathlessness.

Once a young physician, climbing up a steep hill in company with an experienced physician, described to him in rapid conversation his cardiac troubles and palpitations. The older physician replied: "You have a nervous heart and no organic cardiac trouble, else during climbing you would not continue to talk but rather would gasp for breath."

Besides this discrepancy between the high pulse rate and the subjective symptom of palpitation on the one hand, and the absence of symptoms of defective circulation on the other, it is very characteristic that the increased frequency due to muscular work diminishes when work continues and gives way to a normal rate in a few minutes after the muscular exertion has ceased. In organic cardiac failure, as in myocardial weakness, we see that muscular strain provokes also a high pulse frequency, but in addition shortness of breath, cyanosis, sinking of the blood pressure and every symptom of defective circulation, while after the cessation of the exercise a much longer period elapses before the normal pulse rate and respiration is restored.

In closest relationship to pulse rate stands the question of *rhythm*. Does arrhythmia really occur in the nervous heart? It does, but not to any such extent as is generally believed. The only form of arrhythmia whose connection with nervousness we are sure of is the so-called respiratory or infantile arhythmia. Because neither of these names is fully explanatory I propose the name of "changing pulse rate." We understand by this designation a pulse in which periods of more frequent action alternate quickly with periods of lesser frequency, the variations concerning only the duration of the diastole, while the systole and the relation between the action of auricles and ventricles remain unaltered. In healthy people, and especially in children, forced inspiration and expiration produce a slight but distinct increase and decrease of pulse rate. These periodic changes of frequency are developed to a much higher de-

gree in nervous individuals, and it is clear that this changing pulse is nothing else than an exaggeration of a normal reflex, of a reflex whose path and nature are well known, for we are sure it goes over the vagus, and is to be considered a sign of an unstable equilibrium of the vagus center. This symptom belongs to the same series as the exaggeration of the vasomotor reflexes, or of the knee-jerk, so commonly found in nervous individuals. And since such a respiratory irregularity is never observed in organic cardiac diseases, this symptom is of no little diagnostic value.

Regarding the other forms of irregularity it is certain that the pulsus alternans and the pulsus irregularis perpetuus are never symptoms of nervous cardiac diseases; they occur only in cases of severe damage of the heart muscle itself. The pulsus irregularis perpetuus is, according to the investigations of Hering, Mackenzie and Gerhardt, nearly always accompanied by the symptoms of severe injury, often of total paralysis of the right auricle. Since we know the important rôle played by the right auricle in the origin and co-ordination of the heart movements, it is not at all astonishing to find complete arrhythmia as a common consequence of its injury. Rather difficult to explain are the short attacks of complete arrhythmia, even of delirium cordis, which are sometimes found in connection with severe indigestion after overloading the stomach with indigestible food. These attacks can often be checked at once by vomiting or by emptying the stomach with the tube. Perhaps they are to be explained as a form of reflex action through the vagus, or they are perhaps of toxic origin.

By far the commonest form of irregularity is that due to the occurrence of extrasystoles. Does extrasystolic irregularity occur in simple nervous cardiac disease? It is said that it does, and Lommel goes so far as to say that extrasystolic irregularity is so common in young nervous individuals that it is of but little importance. I do not agree with this view and I doubt very much whether extrasystolic irregularities are ever to be considered as a sign of purely nervous disorders. Hering was never able to produce extrasystolic contractions in animals when he experimented on the cardiac nerves, but he admits the possibility that extrasystoles may take place by vasomotor influences if these lead to sudden and considerable rise of blood pressure. In this way we can explain the observation that not infrequently slight extrasystolic irregularities exist in young nervous persons in whom no signs of cardiac disease can be detected. But there is no doubt that in the majority of cases the extrasystolic irregularities are due to incipient or advanced disease of the myocardium, to irritable weakness and to a disproportion between the

strength of the heart and the resistance to be overcome. If extrasystolic irregularity is very pronounced, and if a great number of extrasystoles disturb the normal pulse rate, we are always sure of a severe damage of the heart muscle. If this rule is established, are we then allowed to conclude that a rare occurrence of extrasystolic contractions is but a nervous symptom? Such a conclusion would not be logical.

Yet frequently we observe extrasystolic irregularities occurring over many years before any definite manifestations of a damage of the heart muscle or the blood vessels appear. The extrasystoles may even disappear again completely, especially when such injurious influences as abuse of nicotin, strong coffee, overexertion, or the influence of high altitudes cease, or when the heart accommodates itself by means of hypertrophy to the increase of the blood pressure due to the development of arteriosclerosis. If we are able to follow the fate of individuals who have shown in former years extrasystolic irregularity, we may convince ourselves that not a few of them show in later years distinct symptoms of heart failure or arteriosclerosis, and we draw the conclusion that the evolution of those important diseases often extends over more than ten or even twenty years. Therefore it will be better in practice to consider the extrasystolic irregularity as a sign of importance and not simply as a manifestation of a nervous heart, which commonly passes as harmless.

The nervous heart manifests itself very often by troublesome *palpitation*. Here we would emphasize that palpitation must be sharply distinguished from high pulse rate and that not all sensations which are called palpitations by hypochondriacal patients deserve this name. Whenever we are in doubt whether the patient suffers from true palpitations, have him count his heart beat without putting his hand to his chest, the physician meanwhile controlling his count by feeling his pulse. If the patient is not able to feel every heart beat in his chest and to give its exact rate, then he has no true palpitation but some other sensation which he has wrongly interpreted as such.

In true palpitations the heart throbs violently and shakes the thoracic wall so that the observer may feel it with his hand placed over the cardiac region, nay, see it before the patient has exposed his chest. Shall we assume that in palpitation a greater energy is contributed by the heart to the general circulation, or that a larger part of the expended energy is uselessly wasted in shaking the thoracic wall, energy which in the healthy heart is more economically applied to the propulsion of the blood alone? Tracings of the apex beat are apt to give no explanation of the mechanism of palpitation. They show that the ascending line of the cardiogram is steeper and higher, so we may conclude that the systolic

contraction is quicker, that it reaches its maximum more suddenly, within a shorter time and not in that slow way which is the optimum for the propulsion of the blood. According to our own cardiographic tracings, palpitation seems to be produced by a peculiar type of muscular contraction, and this may be due to certain nervous influences.

The cardiographic tracings in nervous palpitation show a close likeness to those of extrasystolic contractions, which also produce the feeling of a shock to the chest walls. In connection with this peculiar form of muscular contraction we observe the fact that the first sound of the heart is louder and accentuated, and this symptom is not difficult to understand when we remember that Ludwig explained the first sound as being produced by muscular contraction and that the first sound becomes less loud and even disappears whenever the systolic contraction is performed slowly. This is the case in aortic stenosis where the cardiac tracing shows a very slow ascending line.

The apex tracings in nervous cardiac troubles show, besides the quick and high ascending line, no uniformity. Sometimes we see a very pronounced flat or even an ascending plateau; in other cases the tracing falls immediately after the first rise and it is not easy to mark the end of the systole. As Hürthle and Frank have shown, we find the ascending type of cardiac tracings whenever the heart has to struggle against a high blood pressure and when the ventricle finds difficulty in emptying itself. The descending type shows, on the contrary, that the outflow of the blood takes place easily and that the resistance in the vessels is not high. We come to a similar conclusion from a careful examination of the arterial sphygmogram (D. Gerhardt). In cases of nervous heart the sphygmomanometric tracings of the radial artery show a high systolic plateau of unusual duration, sometimes even an anachrotic wave. This may be taken as proof that the outflow of the blood through the capillaries is difficult and slow, and this behavior is coincident with a high maximum of arterial blood pressure and a high minimum as well. There is no explanation possible for this observation other than a constriction of the arterioles and the capillaries by means of vasomotor influence. The same behavior is met with in diffuse angiosclerosis. In other cases of nervous palpitation the sphygmomanometric tracings of the radial show a quick descending line, a high maximum, but a low minimum blood pressure; in these cases the outflow of the blood through the capillaries must be considered as rapid and easy.

This leads us to consider the *arterial blood pressure* in nervous cardiac diseases. In healthy non-nervous individuals the blood pressure varies under changing conditions within strikingly small limits. Even

energetic muscular exercise increases the blood pressure but transiently and then not to a very high degree. The difference between the maximum and the minimum (the pulse pressure) becomes greater, but this is merely a sign that during muscular work a greater quantity of blood is thrown out by every ventricular contraction. In nervous and neurasthenic individuals the blood pressure shows the same great tendency to abnormal variations that we have seen in pulse frequency. Muscular exercise, as well as eating and drinking, especially alcoholic drinks, coffee, tobacco, and, above all, psychic excitement, influence the blood pressure quickly and to a greater degree than in normal individuals. So we often observe in our consultations that the mere sight of the blood pressure apparatus is sufficient to produce a certain fear in nervous patients, and that the first readings give an abnormally high maximum of 160 mm. or more. The blood pressure sinks to a normal figure of 140 or 120 as soon as the patient has convinced himself that no injury will be done to him.

This changeability of the blood pressure is often combined with a tendency to flushings of the head and a disagreeable feeling of heat in the face, to attacks of fainting, to headache, and especially to migraine, to sudden perspiration, to cold hands and feet, symptoms which correspond to the disordered condition of the vasomotor system. In such cases the arteries, especially the radial and temporal, show on palpation a marked contraction at certain times, while some hours later they are found dilated, soft and strongly pulsating.

But in some nervous individuals the blood pressure stands permanently at too high a level. We shall seldom be wrong if we assume that this is a sign of beginning arteriosclerosis. Arteriosclerosis is considered to be the result of continued damage to the vessels, due to too great demands on them. Rapid variations in blood pressure and a tendency to abnormally high pressure are among the main causes for the wearing out of the arterial walls. Thus we may understand why so many individuals, who in their youth have shown the symptoms only of nervous cardiac and vasomotor disease, so often fall a prey to arteriosclerosis relatively early in life. How often this is the fate of charming, warm-hearted individuals, with high spirits, quick intelligence and always ready energy, whose end is nephritis, apoplexy or sudden death from angina pectoris! This evolution from primary pure nervous over-excitability of the heart and vasomotor system into severe angiosclerosis is often observed after severe injury to the nervous system by railway accidents, by great grief and distress, often in widows who have lost their husbands under afflicting circumstances. And whenever we see in such cases of nervous

breakdown that the blood pressure continues to be far too high we are aware that arteriosclerosis has set in.

These few remarks may show the importance of the determination of blood pressure. I believe that in the last ten years no other method has brought us such a distinct progress and enrichment of diagnosis as that of the estimation of blood pressure.

The *size of the heart* fails to show any changes in the majority of cases of nervous heart. Indeed the normal size of the heart has often proved a valuable sign in the diagnosis of the nervous type of heart trouble. But we should not forget that among organic diseases also, especially in arteriosclerosis and nephritis, the heart may show for a long period of years normal size to percussion and to Roentgen rays, although it is quite apparent from the high level of blood pressure that it is continually performing increased work and really must be hypertrophied. Simple hypertrophy without dilatation does not increase the dimensions of the heart or only very slightly. On the other hand, it can not be denied that in cases of long standing and severe nervous overexcitement of the heart the myocardium becomes impaired and that true hypertrophy, sometimes also distinct dilatation, occurs. But here we must refer to a source of error. The violent apex beat of the excited heart strikes the chest wall in a much larger area and therefore frequently simulates an enlargement of the heart which really does not exist.

Among the subjective symptoms of the nervous heart we have to remember *pain* and other distressing sensations in the *heart region*. As long as they do not show the characteristics of true angina pectoris these feelings are of very little importance. True angina pectoris is characterized by short attacks of most intense pain. They appear when the patient walks or when he climbs a staircase and force him to stand still until the pain disappears. Very often the attacks come soon after a rich meal, especially if the patient walks soon afterward; sometimes the attacks occur during the night and awaken the patient from sleep. The pains are localized in the precordial region, behind the sternum, or in the epigastrium, and sometimes may be mistaken for gastric pains; they almost always radiate to the left or the right arm or to the carotid region of the neck. In simple nervous cardiac disease the painful sensations are of far longer duration. They are not dependent on walking, eating, etc., and do not appear during sleep. In most cases they are not at all severe. Usually they are localized in the region of the apex beat, and very rarely radiate to the arms. Very often the patient has the impression that the painful sensations of the nervous heart have their seat not in the heart itself but in the tissues covering the thorax,

and frequently we find a distinctly hyperesthetic area over the skin in the region of the apex beat. If the pressure of the stethoscope alone suffices to call forth expressions of pain from a female patient, then the physician may be sure that he has to deal with a hyperesthetic patient and not with a symptom of true cardiac disease. Though the painful, or better the disagreeable, sensations in the heart region are commonly of but little intensity, they are not to be neglected. By their continued presence they irritate the patient and remind him of his heart the whole day long. As a rule we can say: the more the sensory symptoms, pain or palpitation prevail, the more the psychic factor is pronounced, and the more the patient is subject to the hyponchondriacal idea that he is suffering from severe heart failure.

It is a question whether the well-known symptoms of true angina pectoris or of pseudoangina are met with in simple nervous disease, and whether we should agree with Huchard, Rosenbach and Romberg, who regard attacks of the anginal type as especially characteristic of nervous cardiac affections. Are we able to distinguish a pseudoangina pectoris from the true one, observed in coronary sclerosis and aortic disease? Certainly some nervous patients describe attacks of cardiac pain or even of agony, which makes us believe them to be of great importance. But if the physician happens to observe such an attack personally he can usually convince himself that the attack does not present that elementary convincing severity which characterizes the pains of true coronary sclerosis, but that it is more a feeling of nervous anxiety and oppression. Indeed I am inclined to doubt that there exists a true angina pectoris as a symptom of mere nervous affections. I believe that every patient who has suffered from typical angina pectoris is to be suspected of having some dangerous organic disease and of being prone to sudden death.

It is never wise to make the diagnosis of a purely nervous cardiac disease when symptoms of actual circulatory incompetence are present, i. e., dyspnea, cyanosis, swelling of the liver, diminished quantity of urine, etc. Usually the nervous cardiac and vasomotor disturbances are characterized by polyuria with clear light-colored urine, and very often by the interesting phenomenon of phosphaturia, i. e., by diminished acidity of the urine.

As far as the dyspnea of nervous patients, especially of young people, is concerned, their craving for air and their supposed inability to draw a full breath, the experienced eye of the practitioner should have no great difficulty in distinguishing its true hysterical or hypochondriacal nature.

We now turn to an especially important subject, namely, to the consideration of some other cardiac diseases which show symptoms similar to those of the nervous affections and which are often mistaken for them. I am inclined to say that the majority of cases which in former years have been considered as typically nervous can no longer be placed under this heading.

Here we have first to mention the heart affections in *goiter*. This is very common in the southern parts of Germany and in Switzerland, and from my own experience I may say that nearly a third of all cases of so-called nervous palpitation belong to this disease, viz., to hyperthyroidism. Here I do not mean the fully developed cases of exophthalmic goiter, but those far more frequent cases of incomplete hyperthyroidism where only the cardiac symptoms are very prominent and where other symptoms seldom or never attract the attention of either the patient or physician.

The *"Kropfherz"* (Fr. Kraus) or hyperthyroid heart can be distinguished from the nervous cardiac affections by the fact that the high pulse rate lasts throughout the whole day and night and is not due to reflex action alone. The acceleration in most cases of goiter heart is not excessively great, 90 to 120, not nearly as high as in paroxysmal tachycardia, but high enough to trouble the patient constantly and to make him unfit for all continued work. This effect is due especially to the fact that palpitation is very pronounced. It is worth mentioning that in the hyperthyroid heart as well as in fully developed exophthalmic goiter the increased pulsation is especially felt over the region of the right ventricle, that is, along the left border of the sternum as high as the second interspace, and at the autopsy in cases of exophthalmic goiter I have observed that there was present a marked hypertrophy and dilatation, especially of the right ventricle, and an excessive congestion of the pulmonary vessels. The blood pressure does not depart from the normal. Vasomotor symptoms, flushings of the head and sudden perspiration are very common. If we carefully examine the patient we rarely miss a fine tremor of the fingers and a certain psychic over-excitability. The patients are in a permanent state of distressing mental irritation. They complain that they get tired and worn out by any mental or muscular exertion, and that they are unfit for continued effort. Often we see young individuals who experience difficulty in school or in their occupations in whom hyperthyroidism explains the psychic and bodily deficiencies. Sometimes in the case of young women and girls one is led to suspect chlorosis, but the blood shows normal composition, and the lassitude and cardiac palpitation, in combination with a soft swelling of the

thyroid gland, lead the physician to the right diagnosis. Very characteristic is the liability to lose flesh, even while the appetite is good. In the course of months and years under alternating improvement and aggravation we sometimes see the development of dilatation and incompetence of both ventricles and every symptom of cardiac failure, edema, oliguria and severe dyspnea. The same poison which for many years caused only an increase in the number and strength of the cardiac contractions proves finally deleterious to the myocardium.

The diagnosis of hyperthyroid heart is easy when the thyroid gland shows the characteristic soft swelling, even though this be but slight. The diagnosis is difficult when no swelling at all is present. Yet we sometimes see cases which show every characteristic of hyperthyroidism, though no enlargement of the gland is present. As we may suspect kidney disease when no definite signs are present, so may we believe that a morbid state of the thyroid can exist without any apparent enlargement or diminution in the size of the organ.

In cases presenting diagnostic difficulties we can usually come to a conclusion by a careful administration of the iodids. In cases of hyperthyroidism the iodids, even in the smallest doses, cause immediately a marked change for the worse. They produce an increase of palpitation, a diminution in weight and the appearance of nervous excitement and tremor. I can not agree with those authors who distinguish special types of the goiter heart supposedly due to mechanical pressure by the enlarged gland on the vagus and sympathetic nerve. Rather I am convinced that the goiter heart is an entity and is due to an excessive formation and absorption of the secretion in the thyroid gland. Experiments on the isolated mammalian heart have shown that thyroid extract causes an increase in the number and strength of contractions, and the proof that palpitation, tachycardia, vasomotor symptoms, mental excitement, and the characteristic increase of metabolism are really due to hyperthyroidism, has been given by the fact that the medicinal administration of preparations of the thyroid gland produces in normal individuals the same symptoms, and that in some (but unfortunately not in all) cases of hyperthyroid heart the symptoms are relieved or removed altogether by extirpation of one lobe of the gland. So we may place the "Kropfherz" or hyperthyroid heart among the toxic processes.

Among the poisons which act on the heart there is to be mentioned *caffein*. In connection with this we must consider the excessive use of coffee and tea. Caffein is sometimes used in Germany for the purpose of simulating nervous irritable heart and thus offering escape from military service. Caffein, indeed, when used in large doses, produces exactly

the same symptoms as nervous cardiac overexcitability, strong palpitations and pronounced psychic disturbance.

Tobacco must also be mentioned. I purposely do not say nicotin, for recent investigations make it very questionable whether the toxic effects of tobacco run parallel to its content of nicotin. Nicotin is a strong poison to the nerves, and Langley has shown that it paralyzes the sympathetic ganglion cells. Nicotin acts on the isolated mammalian heart, increasing the rate and intensity of contractions. Tobacco affects the normal heart much less than the nervous or weakened heart. In nervous individuals it produces a distinct increase of the blood pressure. Though chronic abuse of tobacco is surely deleterious to the heart, it proves yet more dangerous to the blood vessels, and in no small number of cases of early and general arteriosclerosis, especially of the coronaries, the abuse of tobacco is the primary cause. Sometimes tobacco seems to produce attacks of pseudoangina pectoris or, as Gibson correctly says, the symptoms of stenocardia without coronary sclerosis. It is possible that a temporary spasm of the coronaries may be produced by the influence of tobacco.

Concerning *alcohol,* we know that it affects the vessels less than the heart muscle, and that the different kinds of alcoholic drinks affect the heart muscle very differently. Decidedly the worst of the alcoholic drinks, as far as the heart is concerned, is beer. The poisonous effects of alcoholic drinks are especially seen in women and children. How often does a woman, a child, a pupil pass for a long time as nervous and affected with nervous palpitation until the experienced physician discovers the alcoholism! It must be noted that in women, in young people and in all individuals with weakened hearts and feeble nervous systems very small quantities of alcohol act deleteriously and produce palpitation. Nervous individuals often show very pronounced intolerance for alcohol. A glass of wine is enough to produce disagreeable flushes and hyperemia of the head, throbbing of the pulse and insufficiency of circulation after any considerable muscular exertion, so that the patients themselves soon realize that they must avoid all alcoholic drinks. But it would be erroneous to suppose that alcohol produces cardiac and vasomotor disturbances and nervous excitement only in women, in young or feeble individuals and in convalescents; it causes the same symptoms also in cases of chronic alcoholism in men. The chronic drunkard very often shows the symptoms of irritable weakness of the heart in combination with general nervous over-excitability, and it is often difficult to find out the true nature and origin of such a "nervous heart" if the patient does not confess his former alcoholism.

When we are considering the toxic agencies acting upon the heart we must not forget the *bacterial toxins*. After infectious diseases, severe scarlet fever, typhoid fever, and especially influenza, there remains often, not only for months but for a year and more, a state of cardiac impairment which closely resembles the irritable heart of nervous individuals. Any excitement or exertion produces an increased pulse rate and distressing palpitation. But muscular work leads in such cases not only to palpitations but also to dyspnea and a feeling of oppression which makes it impossible to continue the work.

The history alone in such cases may lead to the realization that we have to deal not with a nervous heart but with one weakened by infectious disease, although sometimes the patient himself has nearly forgotten that his heart failure dates from the recovery from acute disease. In other words, the injured and enfeebled heart responds to all impulses with abnormal irritability and the "irritable heart" is, so to speak, often nothing else than a weakened heart.

In this connection we must mention also the excessive cardiac irritability and acceleration seen in many patients with *tuberculosis*. The toxic products of the tubercle bacillus act on the heart as well as on the temperature. In cases of debility and of loss of weight, combined with palpitation and slight elevation of temperature, the physician will often find the greatest difficulty in judging whether the case belongs to hyperthyroid or nervous heart or to beginning tuberculosis, especially since tuberculosis in its earliest stages is so extremely difficult to diagnose. Yet it is well to remember that in tuberculosis the heart appears commonly very small in size when examined by Roentgen rays, and that the blood pressure is below the normal level. Tuberculin injections may help the diagnosis. As a result of a prolonged rest cure in tuberculosis we sometimes see that the heart becomes more and more feeble and irritable. Too long continued confinement to the bed or the reclining chair weakens the heart decidedly and makes it unaccustomed to adapt itself to muscular exertion.

The disturbances of the heart which we see frequently in connection with *affections of the sexual organs* deserve especial attention. In pregnancy, especially during the first three months, we not infrequently meet with arrhythmia of the extrasystolic type, which is sometimes believed to be of nervous origin; but, as we have mentioned above, extrasystolic irregularities should rather direct our attention to the myocardium than to the nervous system. We see heart affections manifesting themselves in connection with pathologic processes of the uterus and its appendages, especially in myoma and in inflammatory exudations and adhesions, to

a much higher degree than in the normal state of pregnancy. Cardiac disturbances, tachycardia and arrhythmia appear or increase during the menstruation, and they sometimes pass during this period to actual delirium cordis. If we find in a case of myoma a heart which is not able to withstand chloroform narcosis, which suddenly stops during or soon after operation, and which finally appears at the autopsy as a flabby, soft organ, we may be sure that this is the final stage of a condition which in its beginning had for years wrongly been called nervous cardiac trouble.

In further connection with the sexual organs stand undoubtedly the so-called nervous palpitation, the cardiac and vasomotor disturbances which occur in the climacteric period. Besides palpitation and occasional cardiac enlargement there appear often most disagreeable vasomotor symptoms, which lead to all kinds of falsely interpreted organic sensations and excitements, and the same symptoms may appear, even to a much greater extent, when after the surgical removal of the sexual organs a premature climacterium is produced in younger women. I have often observed in the cases of climacteric cardiac affections that the blood pressure was raised to a high degree.

At the beginning of sexual development, in boys as well as in girls, there often occurs pronounced excitability of the cardiac action, with strong palpitation, and sometimes with enlargement of the area of heart dulness and loud murmurs. These murmurs lead to diagnostic difficulties and to the erroneous supposition of a valvular disease. This *heart of adolescence* may lead to stormy manifestations, especially when the sexual desire undergoes an unnatural excitement and gratification. The heart of masturbation, which Krehl has described, is not a rare thing.

It is rather difficult to explain the connection between the sexual organs and the cardiac and vasomotor system. Is it a reflex mechanism going through the nervous paths or is there an inner secretion from the sexual organs like that of the thyroid or the suprarenal gland? The experiments of the last years, especially those of Starling, give more emphasis to the second hypothesis. Yet we see in all these cases that nervous symptoms are very prominent, sometimes of a hysterical character, and there is no doubt that the sexual heart affections occur especially in individuals with nervous constitutions.

Not infrequently do we see in connection with *obesity* a certain irritability of the heart, often years before the symptoms of true cardiac failure appear. A quick pulse rate is met with particularly in those obese individuals who are unaccustomed to any physical exercise, who drive instead of walk and avoid all muscular exertion. Muscular strain

produces in such patients a high pulse rate, palpitation, and sometimes some cardiac oppression. The patients themselves are very often inclined to think that they are suffering from nervous heart, especially those who do not like to admit that they are too corpulent. But this is not a nervous heart; it is in truth the weakened or *untrained heart* of the unexercised individual. The strength of the heart stands in some relation to the strength and development of the other muscles of the body. A loss of general muscular strength, whether it be due to disease or starvation or to want of exercise, is commonly accompanied by a loss of cardiac strength, and there is no better way to increase the strength of the heart than by carefully regulated general muscular exercise.

We have seen how many pathologic conditions may simulate the nervous heart and how easily an error of diagnosis may arise. Indeed, it must be acknowledged that the more thoroughly a physician examines his patients the more rarely he will come to the diagnosis, "nervous cardiac affection." This diagnosis is only permissible after the exclusion of every other possibility. It would surely be erroneous to deny altogether the existence of the nervous heart, but we must insist that this diagnosis be made only when proof is afforded that there is no failure of the cardiac muscle present, and where the history and examination of the patient shows the presence of general nervous irritability and debility, for only in markedly nervous individuals can we base cardiac disturbances on the nervous system alone, and only then when the cardiac symptoms show the clinical character above sketched.

Paroxysmal tachycardia is rightly included among the nervous diseases of the heart. Suddenly, and often without previous warning, a cardiac frequency of 160 to 200 or more beats sets in, and after some hours or some days the normal rhythm is suddenly restored, often accompanied by the eructation of gas. Paroxysmal tachycardia may represent a primary nervous disease and is then closely connected with migraine and sometimes with its worse brother—epilepsy. I believe that paroxysmal tachycardia is often to be considered as an anomalous or disguised form of these strange diseases, and it shares with them the uncertainty and the hopelessness of therapy. Some fatal cases have been reported where paroxysmal tachycardia was connected with syphilitic changes or other organic derangements in the vessels of the basis cerebri and the medulla oblongata. Sometimes attacks of similar character appear as a complication of already existing organic valvular or myocardial disease. If by chance we can observe the onset of such a tachycardial attack we can readily recognize that first single, and soon more and more frequent interpolated systolic contractions appear during diastole, till finally the

heart rate is exactly doubled or quadrupled. Not only the diastolic rest but also the systolic contractions become very short, and we remember from experiments that the shorter the contractions the shorter becomes the refractory period of inexcitability.

The manifestations of paroxysmal tachycardia can not be otherwise explained than by the hypothesis that through central nervous influence the irritability of the heart muscle increases to a very high degree, although it is not yet possible to explain by what particular mechanism those influences appear so suddenly and disappear at once again.

Every lecture on a clinical subject should conclude with a consideration of *therapeutics,* since all our efforts, scientific research as well as practical work, are directed toward the single aim—to help sick mankind. In the case of true nervous cardiac affections it may be said that treatment which is directed toward the heart itself almost never results in benefit. Indeed, digitalis, caffein, strophanthus and other similar remedies rather do harm than good and they are not able to diminish the increased heart rate and palpitation. Yet there is an exception to this rule; if a primary nervous cardiac disease has finally led to actual cardiac insufficiency, to dilatation, edema and arteriosclerosis, then the above named remedies, and especially also the diuretics, prove of great value.

The treatment of the true nervous cardiac diseases must be directed exclusively against the general nervous condition, and particularly we must try to remove its cause, whether it be overwork or indulgence in excitement of any kind. Above all, we have to remove the patient from the environment, the "milieu," which has provoked nervousness, and that is very often his own family. A sojourn in an agreeable and quiet country place may be of the greatest benefit. High altitudes, such as Switzerland or the Tyrolese mountains, especially are apt to bring great improvement, while the seashore, on the contrary, often proves to have no good influence. The study of climatic influences deserves much attention. Altitude in particular has a most wonderful effect on the heart, the blood vessels and the blood itself, and individuals with nervous constitutions and with cardiac and vascular diseases are very markedly affected by it.

It is not wise to send nervous patients to watering places like Nauheim and to treat them with such measures as carbonic acid baths or alternating electric currents. Such "cures" should be avoided because they prove more exciting than calming, and because they direct the patient's attention too much to his heart, and bring him to the fixed idea that his fears of an organic cardiac disease are correct, and that the doc-

tor speaks of a nervous affection only to console and to deceive him. Very often we see that a nervous and hypochondriacal patient distrusts the physician who simply and truly declares that the heart is normal and the whole trouble a nervous or imaginary one, and much prefers to believe the one who says the heart is seriously attacked, who strengthens the patient's fears and undertakes long and strenuous cures not at all to the patient's benefit.

Sometimes in such cases of hypochondriacal ideas it proves useful to outline the size of the heart by orthography with Roentgen rays, and to convince the patient from this diagram with the centimeter scale that the pretended dilatation is absent. But when we succeed in winning the confidence of our patient we must try to turn his attention away from his heart, to raise other interests and thoughts. For this purpose carefully directed muscular work, gymnastic exercises, walks, and even a little mountain climbing and every kind of outdoor treatment, are most useful. For in the true nervous cardiac affections muscular exercise has not a harmful but a good influence on the heart. Per contra, rest cures which are of benefit in every organic cardiac failure do harm to the nervous heart, really weakening it and making it more and more unfit to adapt itself to any strain. Eventually we may be able so to educate our nervous patient that he learns to keep his feelings and emotions under proper control. This stage once reached he may also be able to command to a certain extent the involuntary emotional movements, excitements and reflex actions of his inner organs so that he may no longer be a victim of their effects.

THE HEMOLYTIC REACTIONS OF THE BLOOD IN DOGS AFFECTED WITH TRANSPLANTABLE LYMPHOSARCOMA.*

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During the course of the present year I reported a series of experiments[1] on the hemolytic properties of extracts from organs and from tumors of dogs. I showed at that time that two sorts of hemolytic substances could be extracted from tumors. One of these, which was present in undegenerated tumors, was thermolabile, and hemolytic only when activated by a substance extracted from the red blood cells. This first substance is comparable to a similar hemolytic amboceptor present in certain normal organs, e. g., kidney. At about the same time and independently it was shown by Friedmann[2] that a hemolytic substance could be extracted from the pancreas, which destroys the red blood cells of the same species, when complemented by some substance (probably of the lecithin group) present in the serum of certain other species. The second type of hemolysin is present only in necrotic tumors; it acts as a simple hemolysin, needing no complement. I ventured to suggest in my first paper that it is the second group of substances which probably passes into the blood, thus contributing to the anemia and the cachexia of malignant tumors.

Since that time I have had the opportunity, thanks to the kindness of Dr. S. P. Beebe, of prosecuting this investigation along somewhat different lines. I have had at my disposal dogs inoculated with the same strain of tumor previously studied, in every stage of its growth. In some the tumors were actively growing, in others they were regressing, while still others were overcoming their tumors as the result of a passive immunity conferred by transfusion. Some of the dogs were in good condition; others were cachectic to the last degree. At the same time I have had a large number of dogs not affected with these tumors, for comparison; some of the latter have been healthy, some cachectic.

It was the object of the present research to study the serum of dogs which had been inoculated with tumors, and to determine whether it possessed any of the hemolytic power characteristic of extracts made

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1. Jour. Med. Research, Boston, 1907, xvi, 287.

2. Deutsche med. Wochschr., Leipsig u. Wien, 1907, xxxiii, 585.

from the tumors themselves. In withdrawing blood from these animals and separating it into serum and corpuscles for further study, the following observation was made: It was generally found that the serum obtained from animals with tumors was stained with hemoglobin, whereas that obtained from animals not having tumors was of the normal straw color. In other words, during the process of separating out in the icebox, the serum of tumor animals had destroyed a sufficient number of its own corpuscles to give it the characteristic tinge of hemoglobin. At the same time, emulsions of corpuscles from the same animals in salt solution remained unchanged, demonstrating that the hemolysis was due not to the lowered vitality of the corpuscles, but to the hemolytic quality in the serum.

The next step was to determine the effects of definite amounts of serum both of normal and of tumor dogs on their own and on other corpuscles. For this purpose, twenty-five dogs in all were selected, of which eleven had tumors and fourteen had no tumor history. All of these dogs were treated in the same fashion. The femoral artery was laid bare under morphin anesthesia, and from twenty to thirty cubic centimeters of blood was obtained from it. The major portion of the blood was allowed to coagulate for the purpose of obtaining serum, while the rest of it was shaken up with glass beads, centrifuged, and made up into a 1 or 2 per cent. suspension in normal salt. The sera, and the corpuscles thus obtained on one day from a large number of dogs, were tested on one another on the following day. One cubic centimeter of serum was always added to an equal quantity of red cell emulsion, incubated for a few hours and transferred to the icebox, where it was allowed to remain over night; the results were noted the following morning. In this manner, 226 separate serum-corpuscle combinations were examined.

A record of one of the experiments will indicate better than any amount of description the type of result which was regularly obtained. The description of the dogs made use of in the experiment, and indicated by numbers in the table, is as follows:

Dog 455.—Four tumors growing slowly for six weeks. Condition good.

Dog 509.—Four tumors growing for two weeks very rapidly. Thin.

Dog 460.—Spontaneous recovery from tumors, which were three in number, and were very rapidly absorbed six weeks before the experiment. Very cachectic animal.

Dog 244.—Tumor almost completely absorbed, owing to repeated transfusions. Dog very cachectic.

Dog 458.—Spontaneous recovery from tumors. In fine condition.

Dogs 516, 517 and 518.—Normal.

Dog 520.—Cachectic. No tumor history.

The following table shows the comparative hemolytic effects of serum from normal and tumor dogs on corpuscles. One c.c. of serum from each animal was mixed with 1 c.c. of corpuscles of each animal, in emulsion. The record of each serum reads along the horizontal line.

	CORPUSCLES.						
	I-455	**2-509**	**3-458**	4-517	5-518	6-516	7-520
Serum **I 455**	—	—	—	v. sl.	v. sl.	v. sl.	v. sl.
Serum **II-509**	—	—	—	sl.	sl.	sl.	sl.
Serum **III-460**	+	+	+	++	++	++	++
Serum **IV-244**	+	++	+	+++	+++	+++	+++
Serum **V 458**	—	—	—	—	sl.	v. sl.	sl.
Serum VI-518	—	—	—	—	—	—	—
Serum VII-520	—	—	—	—	—	—	—

NOTE: — denotes negative reaction; v. sl. denotes very slight reaction; sl. denotes slight reaction; + denotes moderate reaction; ++ denotes strong reaction; +++ denotes complete reaction.

If the table be interpreted in the light of the preceding data, the following conclusions may be drawn from it:

1. The serum of all the tumor dogs is distinctly more hemolytic than is the serum of non-tumor dogs. Of the tumor animals, the two cachectic examples (460 and 244) are more actively hemolytic than are the other three.

2. There is a distinct difference in the resistance of the various corpuscles to the destructive activity of the sera. The corpuscles of the tumor animals are always more refractory than are the normal; they break down less rapidly and less completely.

These two phenomena, the hemolytic activity of the sera and the resistance of the corpuscles of tumor animals as compared with other dogs, dominate the entire series of experiments.

The cause of this difference has seemed to me to be a matter of some importance. It might conceivably be due to a difference in the tonicity or content in electrolytes of the serum, resulting in some obscure manner from the growth of the tumor. In order to determine this matter, each set of corpuscles was in every experiment subjected to the action, not only of a normal salt solution, but also to one of a 0.4 per cent. and one of a 1.6 per cent. strength. It would seem that the degree of anisotonicity represented by these solutions must far exceed that of any serum obtained from a living animal. Nevertheless, the activity of the resulting hemolysis was in no way comparable to that produced by the sera. The general condition of the animals can not be held

responsible, inasmuch as some of the controls were much more emaciated and cachectic than some of the tumor dogs. The hemolytic power of the serum resides, therefore, in some other factor, at present undetermined—possibly the same toxins as were extracted from the tumors in the experiments which I previously reported.

The apparent coincidence of poor general condition and marked hemolytic activity is quite striking, and might at first sight impose as a "*propter hoc*." It has, however, been pointed out that dogs in worse general condition, but without tumors, show less activity in hemolysis. On the other hand, it is perfectly justifiable to interpret the "poor condition" as a resultant of the toxic character of the circulating serum, which manifests itself in the test tube by hemolysing the contained red cells. Two exceptions occurred to the general rules above described. Dog 125, whose tumors had regressed owing to three successive transfusions, in good condition, possessed a serum of slight hemolytic power and corpuscles of slight resistance. Whether this was due to the predominance of normal blood in his vessels, I leave undecided. The second case, Dog 638, normal, has a markedly hemolytic serum, but non-resistant corpuscles. This dog had proved naturally immune to a sarcoma implantation. It may also seem contradictory that dogs which had recovered from their tumors, either spontaneously or as the result of transfusion, should still retain the hemolytic character of their serum to an excessive degree. The fact is, however, in accord with what is known of the clinical absorption of tumors. If, owing to an excessive use of *x*-rays or the mixed toxins, a tumor breaks down too rapidly, its absorption may lead to extreme intoxication of the organism, and even to death. Thus the disappearance of the tumor goes hand in hand with the circulation of the toxic products which have been absorbed. How long an animal may retain these products in his circulation is still to be determined.

The bearing of these experiments on the problem of the anemia accompanying malignant new growths is manifest. They demonstrate that the growth of tumors causes the development of toxic qualities in the blood serum, the exact nature of which has not been determined. It is suspected, however, to be due to the absorption of hemolytic substances previously demonstrated in the tumors themselves.

The bearing of these experiments on the practice of transfusion in curing the tumors of animals, or of men, is important. As is well known, the operation has been performed a number of times in dogs with some success. It is quite evident, however, that to mix the blood of dogs, either of which is hemolytic for the other, would entail the destruction

of a very considerable number of corpuscles, and so would, in part, defeat the very object of the transfusion. There can be no question that the test-tube reactions may be taken as a very good indicator of what would happen were the same bloods to be mixed *in vivo* by transfusion. Of this fact we have had indubitable evidence in the hemolysis resulting after transfusing the blood of one dog into the vessels of another whose serum had been shown to destroy the corpuscles of the former in test-tube experiments. (These experiments have not yet been published.) It is clear, therefore, that every transfusion should be logically preceded by test-tube reactions, and that only those animals should eventually be selected whose serum and corpuscles are mutually tolerant.

On the bearing of the experiments on the subject of human disease I must, for the present, forbear to enter. A considerable number of observations already completed go far to indicate that the results in dogs illustrate conditions which have a parallel in the blood of human cancer cases. On this important point, however, much information must be collected before final conclusions can be drawn.

My thanks are due to Dr. Beebe for his constant encouragement and help during the course of this research.

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TRICHOMONAS HOMINIS INTESTINALIS; A STUDY OF ITS BIOLOGY AND ITS PATHOGENICITY.*

HUGO A. FREUND, M.D.

DETROIT.

Of the parasitic protozoa that infest the gastrointestinal tract, the flagellates merit more attention than is usually accorded them. American observers, who have interested themselves in gastro-intestinal parisitology, and particularly with the monocellular group of organisms, have attached little importance to this by no means uncommon group. English writers, too, have published scarcely any reports of intestinal diseases with which this class of organisms is associated. Continental clinicians, on the other hand, have been more active. Every now and then reports of cases of "intestinal catarrh," "protozoan diarrhea," and the like, find the flagellates playing a not inconsiderable rôle.

The flagellates come under the large group of *Plasmodroma* (Doeflein), and are of the class of *Mastigophora* (Diesing). We find the subclass of *Flagellata* (Bütschli) divided into two divisions of *Monadina* and the *Isomastigoda*. Of the former the *cercomonas* is the representative. The latter is divided further into two families—the *megastoma entericum* (Grassi), typifying the *Polymastigina*, and the *trichomonas* (Donné), typifying the *Tetramitina*. The species of *Trichomonas* that interests us particularly in this study has further been subdivided by some authors according to their morphology or according to the part of the body in which they are found.

We are indebted to Donné, who discovered the parasites in gonorrheal vaginal secretions, for the first accurate description. Trichomonads have since been found in other parts of the body, and in their early history usually associated with some pathologic process. Owing to imperfect observations and, at times, faulty descriptions, these protozoa have been confounded with the *Cercomonas* of Davaine, with the *Megastoma entericum*, and, in one instance, with the *Balantidium coli*. Much of this confusion was due to the inferior methods of observation employed at that time. Other workers, even in recent years, unacquainted with previous work on the organisms, have given them different names, so that many of the reports are misleading.

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* From the Medical Clinic of Prof. George Dock.

Leuckart, in 1863, did more to untangle the conflicting ideas than any one other investigator. But clinicians, particularly, still persisted in naming these organisms after earlier writers. Ekecrantz and Tham's parasites were undoubtedly cercomonads identical with the smaller forms described by Davaine. Marchand found in them a case of typhoid fever and, though without undulating membranes, they doubtless were trichomonads. Grassi endeavored to make finer distinctions than had previously been attempted, and was forced to name some "new" forms. Thus *Monocercomonas hominis* and *Cimænomonas* sprung into the literature. Most of the parasites in his 100 cases were trichomonads. In Leukart's second edition of *"Die Parasiten des Menschen"* we find an accurate classification which the additions of Cunningham in 1881, and Blochman a few years later, did not materially improve on, but substantiated in all important details.

The most important habitats of the trichomonad have been in the intestinal tract and vagina. In the latter place they have never had any pathologic meaning; in the former their presence has given rise to many conflicting opinions as to their significance. Other organs of the body have been infected by them, and much of the interest that is attached to the parasites has grown out of their presence in such localities. Kannenberg, Litten, Streng and Schmidt have found them in tuberculous and non-tuberculous cavities of the lungs. In recent years Rappin, Leyden and Prowazek have come across them in the oral cavity, while in 1904 Theobald and Galli-Valerio observed these flagellates in cases of carcinoma of the jaw. Kruse and Pasquale, Lambl and Cunningham have found them associated with other parasites in cases of liver abscess. A most uncommon and unique case is reported by Hunt, in which the trichomonads occurred along with streptococci in a walled-off perineal abscess. It is only during the past few years that the finding of flagellates in stomach contents have been reported. Hensen in 1897 encountered the trichomonad in a case of carcinoma of the cardia. Since then Strube, Leyden Cohnheim, Rosenfeld and Zabel have met with the trichomonad under like conditions. Emerson believes that it has a distinct diagnostic value in such cases.

It is the occurrence of this organism in the intestinal tract that interests us most in this paper. Ingested with the food, the trichomonad probably thrives best here, in an alkaline medium. For this reason, and because the feces are here in a liquid state, the small intestine no doubt harbors most of these parasites. It is, therefore, in the freshly passed feces in all cases of enteritis that we should seek them. It was especially after Roos' work that more active search was made for flagellates in

diarrheic stools. Though Cahen in 1891 found a cercomonad in a six-months-old babe, Epstein's series in children was the first in which a pathogenesis was strongly suggested. His excellent report on Monocercomonas Diarrhea was followed by the groups of cases of Kruse and Pasquale, Piccardi, and Schürmayer. Janowski's discussion of the subject of flagellate diarrhea in 1897 is the most comprehensive review that has appeared, Skaller in 1898 contributes a case of much interest, and follows with numerous opinions regarding the action of the trichomonad on the intestinal wall. Ucke was the next observer to interest himself in these organisms. He reported the largest number of cases, forty, in which the trichomonad was associated with diarrheic stools. Osborn found the trichomonad in a case from this clinic along with the ameba and two larger parasites. Terry in 1905 is the only American writer, so far as I can learn, who has made any observations on trichomonad diarrhea. The cases that he reported before the Chicago Pathological Society are of importance. During the year 1906 Castellani, Biland and Krause published their observations on several unusual cases. That of Biland is of value especially in that it contains strong arguments for the pathogenesis of the trichomonad. New text-books appearing during the past few years have given more attention to these intestinal flagellates, so that a perusal of many of these will convince one of the growing clinical importance of the trichomonad.

To unravel the faulty nomenclature that has woven itself about the trichomonad, both from the improper regard of previous work and from faulty observations, would be unprofitable. Such terms as *Monocercomonas hominis* (Grassi, Epstein), *Cimænomonas* (Grassi), *Bodo urinarius* (Hassall), *Cercomonas coli hominis* (May) should be discarded. They are all one and the same, and the term trichomonas is fitting for them all. Recent observers have considered the *Trichomonas intestinalis, vaginalis hominis pulmonalis,* etc., different forms. Prowazek, especially, finds distinctive marks of differentiation. The majority of investigators do not agree in this, however, and from the descriptions of authors who have examined the various forms with care I can discover no essential differences. The most striking that I met with were the variations in the undulating membranes that were long in all of my cases and are usually described as extending along only a part of the body in the *T. vaginalis.* I have been unable to get material for comparative study, but, relying on the recent and trustworthy descriptions of Janowski, Dock, Schaudinn, Cohnheim and Schmidt, I am led to the conclusion that we should place all these forms under the genus *Trichomonas* as classified originally by Braun.

Against the fact that these flagellates are the same as those found in lower animals, much evidence exists. Inoculation experiments from man to lower animals, as will be described later, have notably failed. Moreover, their structure is in many ways dissimilar and their mode of reproduction unlike. Hence I am strengthened in the belief that the designation of the entire group of trichomonads found in man under the group of *Trichomonas hominis* is justifiable. The appending of their abode would then be a matter of choice, serving merely as a more complete classification for comparative work.

Morphology.—Though much has been written on the morphology of these parasites, their finer structure still invites investigation. Nor are all the grosser details of these parasites definitely settled. A glance at the many drawings by as many different observers is proof of the insufficient work that has been thus far carried out. In outline the trichomonad resembles, roughly speaking, an apple seed. It departs, however, from this form in a variety of ways, assuming elliptical, spindle, pyriform, irregularly elongated, comma-like and globular shapes. When actively motile, it is continually varying its outline, as it accommodates itself to its surroundings and its direction of motion. The smaller forms preserve the more typical outline, whereas the larger ones generally manifest the more grotesque. The body is perfectly rounded, not flattened as many have observed. Of this I have no other proof than that, as often as I have seen the body, either from its anterior or posterior pole, it has never presented any other than a globular form.

The size of the trichomonad is as variable as its outline. The young forms are the smaller, whereas the mature trichomonads are at times of unusual size. It is of interest to compare the measurements of several observers:

Marchand	13x7.5-9 microns	tail	3 microns
Miura*	17x12 microns	tail	6 microns
Dock	15-22x10-15 microns		
Blochmann	15-23 microns		
Bouchard	10-15x7-10 microns	maximum length	30 microns
Bütschli	up to 40 microns		
Davaine	8-10 microns		
Donné	8-18 microns		
Galli-Valerio	18-19x9-10 microns		
Krause	13-15x7-8 microns		
Leukart	10-15x7-10 microns		
Prowazek	12-24x8-16 microns		

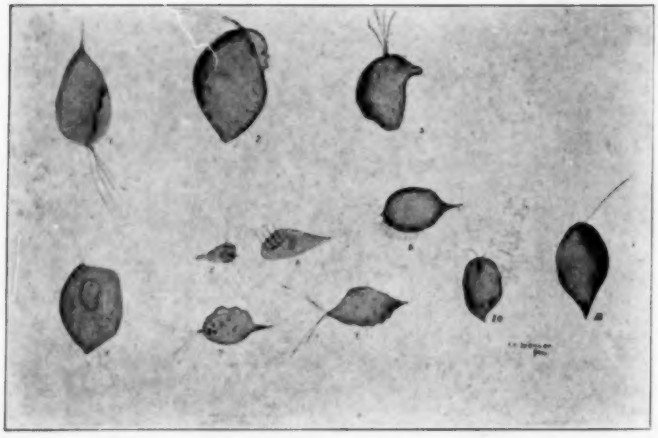
* He gives the flagella from 8 to 10 microns in length.

Accurate measurement is well-nigh impossible in a normal active trichomonad. A loss of motility on its part means an alteration in its vitality as well as form. Then, too, the length of the tail must be

added to that of the body, as the division between the tail and the body can not be determined with certainty in the active form. I have made a series of measurements whose average tallies with that of Prowazek, Dock and Miura. The smallest form that I encountered was 9 microns in length and 6.5 microns in width. The largest was 32 microns long and 19 microns wide. The average organism was 17 microns in length and 10 microns in width. That the same organism, on account of its labile protoplasm, can increase its length and decrease its width and vice versa is obvious.

The organism is distinguished in its active state by the refractive powers of its protoplasm. It has a distinctive sheen not unlike a bit of ground glass, held up to strong light. With highest amplification the protoplasm shows fine granulations resembling very closely the protoplasm of an unstained leucocyte. When the organisms grow older the granules are darker, either coalescing to form more distinct masses, or appearing more distinct in contrast to the minute vacuoles that form in the protoplasm. I have never been able to see a limiting membrane either in living or in stained specimens. When a weak corrosive sublimate solution is allowed to touch the organism the part first affected suddenly coagulates as any albuminous substance will, and gives the appearance of a cuticle. This is but momentary, for the same action quickly extends to the remainder of the protoplasm. There are, however, two distinct parts to the cell that can be differentiated. The ectoplasm is a transparent homogeneous layer. The flagella, the undulating membrane and the tail spring from and are a part of the ectoplasm. The flagella are very delicate, narrow and continuous with the granular ectoplasm in the healthy organism. Carefully stained specimens, under high amplification, show them to be a part of the above named structures that are concerned in the motive powers of the organism. With any of the eosin-methylene-blue stains they assume a pale, grayish-pink hue. The ectoplasm is capable of motility in any part, as is shown by the formation of pseudopodia in some forms during the late stages in life, and it can resist the destructive influence of reagents longer than the endoplasm, and mould the form of the body.

The flagella occupy the anterior or rounded end of the trichomonad. Although Dock determined in the *Trichomonas hominis vaginalis* four distinct flagella, their number in the *T. intestinalis* has been variously given. I have examined a large number of trichomonads to determine the number of flagella, using freshly passed specimens of feces from each of my cases each time. I have never seen an active, normal-appearing organism with more or less than four flagella. While watching an



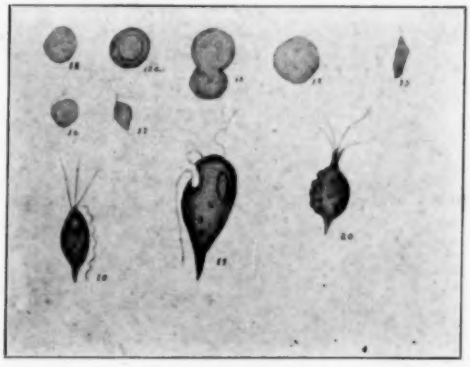


Fig. 1.—1, 2, 3 and 4, trichomonads from bladder (after Dock) stained with methylene blue; 5 and 6, parasite from typhoid stool (after Marchand); 7, after Grassi; 8, after Zunker; 9, after May; 10, after Roos (Marchand's parasite); 11, after Roos (Davaine's parasite); 12, cyst (after May); 12-a, 13 and 14, cyst forms (after Roos); 15, 16 and 17, Lambl's parasites; 18, cimænomonas (Grassi); 19, monocercomonas (Epstein); 20, cercomonas coli hominis (May).

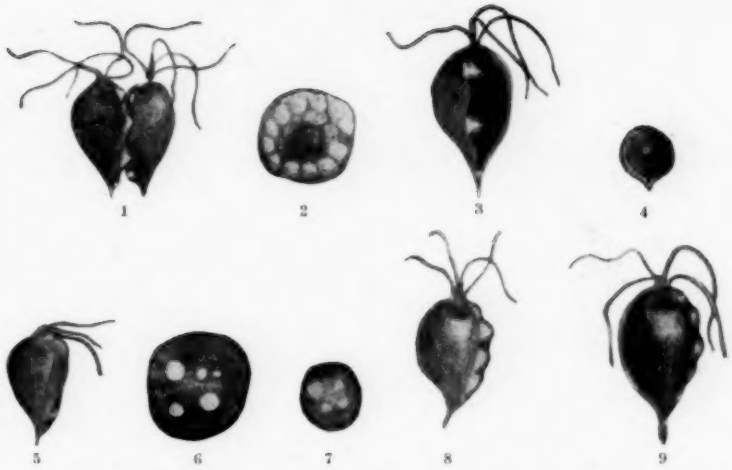


Fig. 2.—Trichomonads. 1, longitudinal division; 2, cyst; 3, 5, 8 and 9, normal trichomonad; 4, spore form; 6 and 7, dead trichomonads.

Fig. 3.—Stained trichomonads. A, ×1380; B, ×1500; C, ×830.

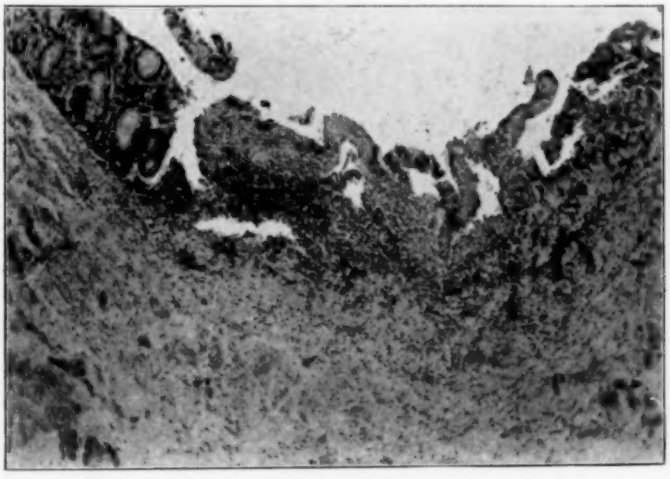


Fig. 4.—Ulcer from colon, ×48.

organism, I have frequently seen it lose one, two, three and even all its flagella. I have seen them become intertwined, giving the appearance of one or two thick flagella, or they have become inactive and dropped alongside of the cell out of focus. I am firmly convinced, however, that every normal trichomonad is possessed of four of these slender lashes at some time during its existence. The flagella spring not from a single point, as some have said, and the remainder taken for granted, but from a small elevated area at the anterior end. Marchand described a rostrum from which they arose. In this I partly agree with him. In the lateral view, in which we see most of the forms, an old and slowly moving form will show the bases of three in a row, the center the most prominent, the two lateral a trifle out of focus. The fourth is invisible, because its origin is opposite the middle flagellum. The ectoplasm at the point of emergence of the flagella is thicker, forming a slight projection. An anterior view shows four distinct points of origin, especially when each flagellum is everted (see drawings). The length of the flagella is variable. They average about nine microns. Roughly, they are as long as the body of the trichomonad itself. They are about one-fourth micron in thickness, and of the same breadth at the tip as at the base. Their ends are rounded. They are homogeneous and impart the same shimmering appearance as does the remainder of the ectoplasm.

Extending backward along the body of the trichomonad in an oblique or curved line from the base of the flagella, to and continuous with the tail, runs the undulating membrane. Its free border is longer than its line of origin. Consequently it lies in folds, giving it an escalloped and plaited effect, which, when active, shows waves running anteriorly and posteriorly. Early it was taken for a row of cilia of varying length. Many of the recent writers describe it as running from one-half to two-thirds the length of the cell. It is seen with difficulty when at rest. Its course is best followed when the organism is moving slowly. When but slightly developed, as in the younger form, it resembles a short fin, occupying only the anterior third or less. During the life of the few organisms that I have been able to follow, however, the entire membrane has been visible at some time during its existence. On the other hand, I have seen a fully developed membrane become rapidly smaller as if some contractile power of the ectoplasm lessened its length and breadth. In older forms the membrane becomes lax and loses some of its high state of contractility. This can frequently be seen in the pseudopodia that are projected. These come from the membrane, but I have seen them in a few specimens as projections of the ectosarc itself. There is never any inclusion of the endosarc in these protrusions. Hence I am in-

clined to regard them as an evidence of oncoming dissolution and not of a physiologic function, such as is seen when the organism puts forth a portion of its entire protoplasm.

The tail of the trichomonad, structurally, resembles and is a part of the undulating membrane. It varies in size from a tiny protrusion to a well-marked appendage. The longest measured a trifle over 6 microns. It is conical in form and tapers down to a fi[illegible] filament in most cases. In fewer instances it has a blunt end. At times it is absent, and, though I have never seen it absent from all the organisms for days at a time (as Dock saw in *Trichomonas vaginalis*), I have seen many examples in which the caudal end was perfectly round, with neither vestige of the old nor sign of the new tail.

The endosarc is the granular inner portion of the protoplasm and is composed of two parts. The hyaloplasm in the normal organism has a pale, grayish green shimmer. Scattered through it are many fine granules, with a few coarser, irregular masses in the central portion. Contracting vacuoles, though described by some, have never been met with in any of my specimens. Just prior to death vacuoles of all sizes are numerous, these coalescing after death to form one or more larger clear areas in the protoplasm. The nucleus, which is from one-fifth to one-sixth the size of the body, is situated in the anterior or rounded end of the trichomonad, a short distance posterior to the flagella. It is usually oval, with its long axis obliquely placed. The nucleus is surrounded by a distinct nuclear membrane. It is composed of coarse chromatin masses and contains, in most instances, a distinct nucleolus. When treated with corrosives or fixatives, the nucleus becomes more distinct and globular. The nucleolus is then seen as a dark elongated mass.

An alimentary canal has been ascribed to the trichomonad by some observers. Davaine claims to have seen an oral cavity near the anterior end. Künstler described an alimentary canal consisting of a mouth and gullet. Others were unable to find it. Epstein, though he claims to have seen a mouth opening at the anterior end, admits he never say a trichomonad engulf food. Bouchard says there is a mouth a little beyond the base of the flagella. It gives access for a tube of a definite length, terminating in granular protoplasm in which one can see many small colorless vacuoles. Dock speaks of a "shallow depression or cleft near the insertion of the flagella, which no doubt has the function of the mouth." He admits that it is uncommon. There is no doubt about the presence of a small depression near the flagella. This I have considered to be part of the undulating membrane dipping down before its first wave appears. It can be seen when the body is turned at such an angle that

this trough in the membrane assumes the appearance of a depression or cup. I have seen no esophagus nor granules or vacuoles at the base, as described by Bouchard. The manner in which the trichomonad gets its nutrition has been variously explained. It is possible that a pseudopodial action assists in engulfing minute particles and bacteria. Or there may be a set of minute openings whereby pabulum can be drawn into the cell body. The only other method is by a process of absorption and osmosis whereby the nutrient substances are continuously being taken directly into the organism. Aided by its flagella (which set up a vortex that swirls toward its body) and undulating membrane, an ever-changing current sweeps about the trichomonad. I have never seen bacterial or other inclusions, nor have any observers given positive proof of seeing such organisms in the act of feeding.

Before taking up the additional features disclosed in the stained specimen, a short description of the various methods employed to stain these organisms will be necessary. Litten first succeeded with a combination of eosin and methyl violet. All but the nucleus was stained. Streng, in working with the infusoria that he found in cases of lung gangrene, was unable to stain them, but found that Lugol's solution brought out their flagella. Dock and Janowski, in 1896, experimented with many reagents and dyes. The former found that staining living specimens or specimens recently killed with weak corrosive sublimate gave the most satisfactory results. All the other fixatives worked poorly. Bichlorid of mercury kills the organism instantly, but produces changes in the protoplasm that alter the true picture. Staining with methylene blue destroys the protoplasm still further and increases the number of artefacts that have sometimes been described as exceptional characteristics of the trichomonad. Acetic carmine may be employed to bring out the nucleus with good effects. The nuclear membrane, which is made especially distinct by this method, has been questioned by some observers. Galli-Valerio has used carbolic fuchsin with excellent results. Prowazek used neutral red, a dye that had previously been considered inferior by other workers. He states that in one specimen he found fourteen cocci in a cell. Ucke, in 1903, employed thionin-eosin. The nucleus stained red by this method, and better differentiation was obtained than with any previous method. Krause, in 1906, used May-Grünwald, staining but one specimen at all satisfactorily. This one good result with a triple stain was proof positive to me that by modifying our methods success must eventually follow its use.

The trichomonad has several peculiar properties. It disintegrates immediately on death of the organism and drying kills at once. There-

fore, to stain the parasite of the intestinal tract, immediate staining, following quick fixation, are the requirements that must be fulfilled. It is first necessary to mix some thin fixative with the stool rich in trichomonads. Egg albumin suffices. Drying a thin, rapidly spread film with the aid of a moderate degree of heat is best. I employed almost every kind of fixative—heat, absolute alcohol, methyl alcohol, ether and alcohol, osmic acid, corrosive sublimate and formalin. Of these, none gave more unqualified satisfaction than the fumes of 1 per cent. osmic acid followed at once by one of the polychrome dyes in a solution of methyl alcohol. I used Romanowski, modified Romanowski, Wright, Giemsa and MacNeal mixtures, all modifications of the polychrome stains. Wright's stain gave the best results, because I was more accustomed to manipulating it and because of the rapidity of its action. In this manner I was able to obtain stained specimens of the trichomonad, staining differentially the nucleus, protoplasm and appendages. I have been unable thus far to stain an organism in its normal form. As the drawings and photographs indicate, they become globular, a few remaining pyriform. This is readily explained. The moderate warmth and rapid drying of the film does not kill the organism, as can be demonstrated by quickly examining such a partially fixed specimen with a one-seventh objective. The organism has lost some of its activity, however. Then follows immediate fixation and drying with the fumes of osmic acid. The alcohol of Wright's stain further fixes the trichomonad, so that it is stained in that form.

Examination of the stained specimen reveals new facts. The protoplasm is dyed a deep blue and contains a few irregular vacuoles due, no doubt, to fixation. The nucleus occupying the anterior portion of the cell is stained deeply by methylene red, the chromatin resembling closely the nuclear material of a malarial parasite. It is dense, closely packed, and occasionally a darker area situated to one side suggests a nucleolus. The appendages are very pale. The undulating membrane can be seen in relatively few instances. It stains a grayish pink and continues into the tail, which stains a similar color. The tail tapers off gradually, sometimes extending out into a long thin filament. Anteriorly the flagella appear as pale, drab-colored, fine filaments springing from the ectoplasm as it is seen extending forward from the membrane. They lie close alongside of the body wall.

The trichomonad is one of the most actively motile of the monocellular parasites. It has three different kinds of motion. The first is quick and jerky and has no constant direction. The second is due to the activity of the appendages and by its aid the organism swims about.

The third is pseudopodial. The trichomonad not only employs its flagella, undulating membrane and tail, but the natural contractility of the protoplasm is perpetually altering the shape and position of the organism in the field. This power, I believe, lies in the ectoplasm mainly, and acts in conjunction with the appendages. Of these the flagella are the most active. When the organism is at rest, they float in wide curves in front of or at the side of the cell body. But when motion begins they start from the extended position and sweep down the body of the trichomonad in a snapping, whip-like manner. They alter this motion frequently in that two act together on one side, or one or more remain inactive. It is in this way that the flagella, flapping against the side of the organism, set up currents that aid in propelling it forward. As each contraction beginning in the flagella sets up its wave, it simultaneously transmits this wave to the undulating membrane. Thus the wave travels from the anterior pole of the cell quickly backward in from three to six undulations into the tail. These waves, started in rapid succession, keep up incessantly, and give the membrane an appearance not unlike flowing water. The undulating membrane has several purposes. It keeps an ever-changing current of fluid about the body; it acts as an organ of locomotion in a small degree, and serves as a keel at times. The tail takes an active part in locomotion. Both by virtue of its long tapering end and its power it forms the most active organ of propulsion. This is especially borne out by the diminished activity in those forms that have lost their tails.

The trichomonad has a further function (described by Marchand in 1875), that of putting forth pseudopodia. This process differs from the prolongations of the ectoplasm previously described. It occurs but rarely in the intestinalis, though it is often seen in the vaginalis. The pseudopod consists of a prolongation of both the ectoplasm and the endoplasm. It is protruded slowly and usually remains as a projected part of the protoplasm for some time. It does not have the flowing motion as is seen typically in the ameba, and it retracts again very slowly. Prowazek has observed these protrusions in the *Trichomonas lacerataæ*. In his instances the nucleus, undulating membrane and flagella divided before the protoplasm was finally constricted. He believed it to be a process of direct division. Dock described some very pretty examples and ascribed the function of pseudopodial formation to that of nutrition. I have sought diligently and have seen but an occasional poor specimen in an old cell. These organisms soon died, so that I can neither affirm nor deny the views of either observers as to the function of the pseudopod.

The trichomonad is susceptible not only to chemical reagents, but heat and cold also markedly influence it. It can live in slightly acid, neutral or alkaline media. Heat of 45 degrees C. quickly kills the organism. Cold has the same effect in that the organism lives but one-half hour at 20 degrees C. The longest I have ever been able to keep any alive and active on a warming stage has been forty-two hours. Placing some of the infected material in an incubator, a few sluggish forms could be detected at the end of sixty-six hours. Unlike amebæ, these organisms do not respond to the slight heating of the slide on which they are spread after their motility has once diminished. The first sign of oncoming death of the trichomonad is a lowered motility, especially in the short, quick, characteristic jerky movements. Then follows a lessening in the activity of the appendages. The flagella are seen in any position waving irregularly. The undulating membrane becomes more distinct and its waves are slower. The tail ceases motion, too. The body assumes a more globular shape and masses of the protoplasm heap together to form darkened areas. Vacuoles appear in contrast. These soon coalesce to form larger, clearer areas. Soon the membrane disappears, together with the tail and the flagella. The cell becomes darker, denser and more globular. Suddenly it plasmolyzes and seldom a vestige of the cell remains.

It is impossible to cultivate these organisms. Growth under anaërobic conditions has so frequently failed that I made no further attempts. I tried, however, a process of fishing for these organisms with a fine platinum wire under a one-fourth power objective, and transplanted them to a culture medium of coli communis of *proteus vulgaris*, and of the mixed growth. I incubated two, six and ten hours. I was unable to find them afterward in any instance. Then I tried to transplant them to the mucosa of the gut of a sheep and of a pig by transferring loopfuls of fecal material rich in trichomonads to the partly cleansed gut of these animals, kept in a moist chamber at body heat. Here, too, my parasites died. Finally, I endeavored to infect the alimentary tracts of numerous animals, employing the cat, dog, rabbit and guinea-pig. I injected small amounts per rectum and also mixed fresh material with their food at various times. No diarrhea resulted, nor could I find trichomonads in the subsequent passages of these animals.

The important question now arises as to how these parasites reproduce if they are so short lived outside of the human body and no trace is left of them after death. It has long been known that direct division is common among all monocellular organisms. Monocellular parasites also have the power, after passing through a definite cycle, of forming bodies

more resistant than themselves that are readily disseminated, and capable in proper soil of forming new adult organisms. The flagellated are not the lowest in the scale possessing this power of reproduction and propagation. They possess both the power of direct cleavage and cyclical division or "spore building." It is not uncommon to see splitting take place in the trichomonad. Fresh specimens, on a warming stage, frequently show forms in different degrees of division. Lambl, in 1859, probably was the first to see dividing occur, though his description is vague. Pfeiffer, Künstler, Cunningham, Bouchard, Marchand and other observers describe division quite accurately, they having seen it take place in specimens from the stool, urine and vagina. It occurs with varying frequency. The cleavage is longitudinal, there being equal splitting of the undulating membrane, as well as of the flagella, tail, nucleus and body.* It requires from forty minutes to one and one-half hours for complete division to take place. As soon as the parasites have become partially divided, a continual tugging motion is set up until finally they split into two small active forms and swim away rapidly.

Though much doubt exists in the minds of many investigators as to the existence of a definite cycle, the formation of cysts or spores has been quite generally observed. Nothnagel, in 1881, so far as I can determine, first described cyst forms or "Dauer-sporen." He thought they were dead monads. Perroncito, in 1887, claims to have seen cyst formation. The trichomonad dropped its flagella and tail, became globular, and a dark exterior and a light interior became differentiated. Roos, in 1893, speaks of encysted forms that appeared in one of his cases when the stool was free from motile forms. These were small, round, refractive, greenish bodies, sharply outlined, immobile and with no inner structure. They varied from 5.5 to 7.5 microns in diameter. He also saw larger bodies, 14 to 17 microns, with distinct cell contour or double membrane, containing small, round, greenish bodies. These were found on various occasions in the stools.

Contrary to these observations, Schmidt and Strassburger claim that cysts are not known. Epstein saw neither division nor cysts. Dock, though never having observed such forms, admits their possibility, saying, "it seems there must be some other method of reproduction than that by division." In recent years several workers have seen spore bodies. Galli-Valerio saw cysts in a patient in which trichomonads were found in a cancer of the jaw. Theobald had a similar case. Ucke demonstrated that besides ordinary encysted forms, stages could be made out

* Prowazek has noted a division into three in a form *Trichomonas lacertæ* closely resembling and allied to the *Trichomonas hominis intestinalis*.

in cyst formation. In changing to the encysted form he saw the trichomonad lose all its appendages and become round and later become oval again. I have frequently seen cysts in all the cases that I had the opportunity to examine. I have never seen similar bodies in non-infected feces. They appear in increasing number, a few being seen one day, a great many the next, and the number then diminishing till no more are seen. Their appearance is not periodic. Contrary to some earlier observers, a cyst does not imply a single encapsulated trichomonad capable of resisting severe influences and evolved solely for the preservation of the species. A cyst is a heavily encapsulated body containing two or more (up to twenty) small pale, greenish, shimmering spores about a central mass of cellular material, capable of spreading after rupture of the wall. From these small spores the adult trichomonad finally develops.

Just what causes the trichomonad to undergo cyst formation has been in doubt. Whether copulation takes place or not, only continued observations can determine. Schaudinn, in 1903, mentions the union of two parasites. Previous to copulation the organisms lost their flagella and moved about by pseudopods. They united and their nuclei underwent several reductions from which cysts resulted. Krause last year described propagation of the trichomonad by copulation. Usually a larger form seized a smaller one, during which the flagella were intertwined, thus uniting the organisms by their anterior ends. After several efforts on the part of the smaller form to separate from the larger, the two remained together from three to six minutes, moving actively all the while. The nucleus gradually sought the periphera and showed lively motion in its center. After several futile attempts the smaller tore itself from the larger and slowly moved away. The larger, meanwhile, showed unusually energetic motion. Here his description ends, no further mention being made of what became of either form. This observation of Krause I can substantiate by several that I have had the good fortune to witness in my cases. I have not seen the approach of the nucleus to the periphera, nor have I seen any interchange of nuclear material. The changes that took place after the separation of the two forms interested me mostly, in that the formation of cysts was thereby explained.

I was able to observe one specimen on the warming stage in which two organisms, one smaller and one larger, united by their anterior ends. After active tussling motions for about four minutes, during which time both lost their tails and undulating membranes, the two forms separated, the smaller one floating to one side and the larger remaining quite active in the field. This motion presently became less,

when darker masses of protoplasm could be seen dancing throughout the cell. These soon collected in the middle, the outer part being taken up by globular, highly refracting greenish bodies. The cell was now motionless. The membrane was distinctly double. There was a small indentation at one edge, but I could not determine its nature. I have seen similar notches in many specimens since. With the view of determining what would become of the cyst, I watched it for six hours without noting any changes in its shape, size or activity. Cold water was run through the chamber of the stage without any effect. While allowing hot water to flow through I accidentally lost this cell. Since then I have applied heat to similar bodies. The first action is to cause them to swell up. Suddenly the membrane breaks and many little spores are set free. These soon die, probably from the effect of the heat. I have observed, from time to time, however, in infected stools, the presence of small, round, highly-refracting bodies with a single flagellum. They are from 4 to 7.5 microns in diameter and move about fairly rapidly. I have watched these for hours, but have never been able to keep them alive long enough to observe any other change in them but a decided growth and partial elongation. They suggest to me, however, young spores that have become active.

This brings to mind an observation of May, made in 1892. He is certain that on the warming stage smaller forms with one flagellum and rapid ameboid movement are transformed into adult trichomonads. Their bodies lengthen to form a tapering end; projections of the protoplasm slowly appear, following which they take on a more rapid motion. Gradually an undulating membrane forms and suddenly flagella appear. May adds that he did not see the reverse take place. Whether the foregoing observations are the fragmentary evidence of a sexual cycle, diligent and accurate work in these forms will alone determine.

During my studies on the trichomonad I had the opportunity of observing the clinical course and symptoms of ten cases in which these organisms were discovered in the feces. These patients came with a variety of complaints, some relating solely to intestinal disturbances, others presenting the picture of some organic disease. A short outline of each of these cases will be given for the purpose of determining, if possible, the influence of the trichomonad as a causative factor in enteritis.

CASE 1.—The first case of this kind was in a male, aged 42, a photographer, who came to the medical clinic complaining of weakness on exertion, shortness of breath, pallor and diarrhea with watery stools. His father died of "bowel trouble"

after one day's illness. His mother died of "nosebleed." No other history of importance was obtainable. Eighteen months previous to his admission (Jan. 26, 1906) the patient began to notice a change in his color and some loss of weight. In twelve months he lost sixty pounds. Three months ago his appetite began to fail him and weakness on the least exertion became pronounced. The swelling of his ankles has been recent. The diarrhea is of six months' standing. The passages are not frequent, but are thin and watery at times. He has noticed "slime" in his stools, but never any blood. No tarry stools. There is a slight, constant pain in the rectum, but never any tenesmus. He has had intervals of cramping pain radiating all over the abdomen. At these times he did not note any exacerbation of the intestinal symptoms.

The important features of the physical examination were the weak, flabby muscles, the lemon-colored, wax-like skin, the extremely pale mucous membranes, the bluish tinted sclerotics and the moderate edema of the lower extremities.

Spleen, liver and kidneys not palpated. Rectal examinations showed a few small hemorrhoids, but no ulceration of any kind. The mucosa was very pale.

As the blood examination showed, the patient was suffering from pernicious anemia in a severe form, red blood corpuscles 992,000, leucocytes 2,150, hemoglobin 23 per cent. A differential count gave 34.9 per cent. of small lymphocytes, 1.8 per cent. of large lymphocytes, 3 per cent. of transitionals, 62.7 per cent. of polynuclear neutrophiles, 3 per cent. of mast cells. There were many microcytes, macrocytes and poikilocytes. One megaloblast and eight stipple cells were seen.

The urine on admission was acid, dark reddish yellow, 1.014; no albumin; no sugar; no bile. A strong test for indican was present. The white, flocculent sediment was composed of leucocytes, a few squamous cells and bacteria.

Test meals revealed achlorhydria, apepsia, a rapid motility, and a slight excess of mucus.

The stool examined on February 2 was as follows: About one-half pint of light brown stool of creamy consistency, containing small flakes of mucus; no macroscopic blood nor food particles. Occult blood tests were negative. Microscopically, many triple phosphate crystals; no Charcot crystals; some vegetable and some muscle fibers. A large number of trichomonads and many cells, from four to six times the diameter of a red blood cell, showing a clear, hyaline, outer margin and numerous small round vacuoles were present. Some of them have brownish pigment, but none have red blood cells in them. No red blood cells were seen in the spread; many leucocytes and small epithelial cells; bacteria very numerous.

The patient was given small salines daily, followed in an hour by a liter of warm water containing fifteen grains of quinin sulphate. The patient had some difficulty in retaining these enemas, and they were later discontinued. Hydrochloric acid, twenty-five drops, after meals, and "anemic" diet were ordered.

The patient did not show any perceptible improvement. The progressive anemia could not be checked. Some of the more important data in his case are given below.

February 7.—Patient had six stools yesterday. The general character has been light brown fluid and with a distinct dysenteric odor. There has been much mucus. All contain ameba coli and trichomonads, the latter in great numbers. They vary in size from 6 to 12 microns in body length, with long tapering tails. In one field six bean-shaped bodies are seen, measuring 10 by 12 microns, nonmotile, and containing many small granular bodies and a single vacuole. They resemble spore bodies.

February 11.—The patient showed some slight improvement, gaining both in strength and in appetite. The blood examination was in all respects the same as

at the first. The number of his stools became fewer from that time on, the trichomonads being less numerous and the mucus disappearing.

February 21.—The patient complained of feeling chilly this afternoon. He had a slight rise of temperature, which later rose to 103.2.

Stool Examination.—There are many live actively motile ameba. There are two types of trichomonads. A larger type described before and a smaller form measuring from 3 to 5 microns. These small organisms show different motions than the larger ones. They possess quick, jerky, protoplasmic motions, running first in one direction and then in another. They have two flagella. The nucleus is in the center of the cell. There is no undulating membrane. These trichomonads were in excess in the stool at 2 p. m. At 5 p. m. but few of the larger ones were to be seen. In the last passage all forms are absent.

The patient's rise in temperature continued. He became much weaker, the stools were on an average of four a day and contained many parasites of all types. On the 24th the red blood cells numbered 744,000; white cells, 2,000; hemoglobin, 9 per cent. (?). Differential count showed 53.8 per cent. of small lymphocytes and 45.8 per cent. of polynuclear leucocytes. There were many misshapen cells, 13 megaloblasts in 500 cells counted, a few stipple cells and much polychromatophilia.

On the 26th the patient had a severe nosebleed requiring plugging of the left nares. This loss of blood did not cause any marked change in the blood count. About this time a diffuse swelling appeared about both eyes that was at first taken for edema. The following day it was noticed that this spread in all directions on the face, with a slight line of demarcation. There was no redness and only a moderate amount of induration and tenderness. There was no rise in the leucocyte count, but the differential count showed a marked rise in the polynuclear forms.

The patient gradually became weaker. He had numerous attacks of epistaxis. His stools were more frequent, and soon were passed involuntarily. His heart weakened suddenly, and on March 4 he died. An autopsy was performed by Prof. A. S. Warthin, to whom I am indebted for the notes and specimens.

The pathologic diagnosis is all that will be necessary in this case. There was progressive pernicious anemia; hyperplasia of bone marrow, pulp of spleen and hemolymph nodes; hemosiderosis of spleen, liver and hemolymph nodes. Lobular, fibrinous pneumonia of the left lung. Congestion and edema of the right lung. Cloudy swelling and fatty degeneration of heart muscles, liver and kidneys. Central zone of necrosis of liver.

Stomach small, contains small amount of yellow-gray fluid of sour odor. Tenacious mucus covers the atrophic mucosa. Small intestine contains slight amount of light-yellow, semi-fluid, tenacious material; considerable edema of submucous tissue. Muscular coat is thin. Marked congestion of caput coli. Large intestine: many small bits of mucus, many of them blood-stained. Walls very thin in upper two-thirds. There are numerous superficial ulcers, irregular, circular and oval in outline. The margins are raised. The bases are smooth, consisting of whitish granular material, 4x6 mms. in diameter. Lower one-third free from ulceration.

On microscopic examination of fresh material from different portions of the intestine trichomonads were found, chiefly in the small gut and mostly in the upper portion. There were some in the large intestine, especially in the granular detritus covering the erosions. Some amebæ were present throughout the entire tract. The mucosa of the stomach showed slight round-celled infiltration. No atrophy. The mucosa of the ileum was slightly atrophic. The epithelium of the mucous lining of the colon was absent. There was round-celled infiltration. Typical small ulcers. Some hyperplasia of connective tissues about the ulcers.

CASE 2.—The second patient came to the medical clinic June 2, 1906. This patient was aged 35, single, an engineer by occupation. His illness began with cramping pains in the abdomen, dull headache, and malaise. The patient lost his appetite and was nauseated at times. From this he slowly recovered. Three weeks later he was seized with severe pains in the right side, at the margin of the ribs, which radiated over the entire abdomen. The pains were periodic. No vomiting and no jaundice at any time. Stools were yellow and had a sour odor. There were from three to five movements daily. The patient weakened very rapidly and was unable to move about without assistance. At this time the patient was brought to the University Hospital. Abdomen was on the level of the ribs, lax, with peristaltic movements clearly visible. No painful points, but a diffuse tenderness on superficial as well as deep palpation. Spleen, liver and kidneys not palpable. Rectum negative.

Urine: Specific gravity, 1,024; acid and reddish brown in color. No albumin; no sugar; no bile; indican in large amounts; no diazo reaction; sediment small, composed mostly of urates.

Blood: Red blood corpuscles, 3,550,000; leucocytes, 11,240; hemoglobin, 80 per cent.; Widal reaction negative.

Stool: Medium sized, light brownish yellow, with a distinctly putrid odor. Faint occult blood reaction obtained. No macroscopic blood. Small bits of mucus, in which are found large numbers of actively motile trichomonads. Some undigested starch.

The patient's condition remained about the same. He had slight, daily rise of temperature in the afternoon, occasionally reaching 102.5. The soreness in the abdomen persisted, the stools continuing to have all the characteristics described above. The blood appeared at times while the patient was on a strict diet. He became steadily more anemic, however. He lost nine pounds the first week in the hospital, and continued to lose for the following three weeks. The patient was then put on frequent, small doses of salol, and was given cool enemata. His diet was light, and he was kept in bed and out of doors most of the time. About July 1 the pains disappeared and he became brighter. His appetite improved, and the movements became natural. The trichomonads were present, but in much fewer numbers, being absent for days at a time. He left the hospital with instructions to continue treatment, fresh air and rest. He gained in weight up to 160 pounds, returning to his work in October. He has had two periods since when he experienced attacks of constipation alternating with diarrhea, with cramping pains in the abdomen, lasting, in all, one week. At these times he describes the stools as being of the same gross appearance as those he passed during his initial illness.

CASE 3.—J. H. B., aged 62, farmer, came to the medical clinic Nov. 11, 1906, complaining of colicky pains in the abdomen, and diarrhea. At the age of 18 the patient went to war and served in the Union army for a period of two years. The diarrhea, of which he complains now, began during his service while in Tennessee. All the men in the ranks had attacks of what the physicians of the regiments then called "mild cholera morbus." They assigned this to the water, which was often procured from pools and ponds. The diarrhea which he experienced in the service was accompanied with some sharp, griping pains, but how long these lasted he does not remember, for he was wounded soon after.

He has had repeated attacks of diarrhea ever since. These come from twice to three times a year, and last for a month or six weeks. In 1892 the patient had a very severe attack, of short duration, during which excruciating, cramping pains in the abdomen and very frequent passages kept him confined to bed for two weeks. He lost in weight and strength at this time. Subsequent attacks were less severe until 1902, when gastric distress complicated the diarrhea, which grew

worse in proportion. The present attack began about four weeks ago and the patient is about recovering from it at the present time. He has had from five to six stools a day, very loose and watery, not of a very offensive odor, but apparently containing much undigested food. At the height of the present illness the patient had from fifteen to sixteen stools during the day, with incontinence of feces at night. There were some pains of a colicky nature, but these have subsided. He passes little or no gas. No pain with defecation. During this last attack the stomach symptoms became aggravated. The distress in the epigastrium, of which he complains, is relieved, however, by going to stool. Physical examination is negative.

Blood: Red blood corpuscles, 5,240,000; leucocytes, 6,170; hemoglobin, 100 per cent. Of 615 white cells counted, 14.3 per cent. were small lymphocytes, 13.1 per cent. were large lymphocytes, .3 per cent. transitionals, 65.2 per cent. polynuclears, 2 per cent. eosinophiles, 1.1 per cent. mast cells, and 4.1 per cent. degenerates and undetermined cells.

Urine: The twenty-four hour amount was scanty. The specific gravity was never below 1,021. Acid; no albumin; no sugar; moderate sediment of urates at times. There was always a strong reaction for indican.

Stomach: The patient's stomach showed a lack of free hydrochloric acid, at times, and a diminution in the ferments. There was an increase in the motor power, with an excess of mucus and the presence of non-motile rods and cocci at each examination.

The patient was put on an intestinal test diet at once, and his stools were examined. The first day he had five passages. The stools were thin, light yellow, and granular. No macroscopic food remains. Microscopic examination of small bits of thin mucus revealed a large number of active trichomonads with some round, less motile and darker bodies. Occult test negative. The patient was then given a large dose of Carlsbad salts, which was followed the next day by one very large stool and two smaller ones. Enormous numbers of trichomonads were found. No blood. The third day he had four passages, the trichomonads being still quite numerous. In the last passage, however, there were fewer than there had been at any time since his admission. The remaining four days that the patient was in the hospital he had but one thick and unformed passage each day. The trichomonads were present, but in very much smaller numbers than before. The griping had disappeared and the patient's strength returned. He was sent home and advised to take saline cathartics twice a week, following repeated small doses of calomel. He has had no attack since.

CASE 4.—G. C. presented himself to the medical clinic complaining of pain in the "stomach" and "bowels" and a violent headache. He dated his present illness to four years previously when he had a similar attack. At that time he had severe abdominal pain and diarrhea. He had about twelve passages the first day; after that they became fewer. He kept about for a couple of days, but his fever rose to 105, so he went to bed, where he remained for three weeks. During this time he had severe continued pain in the lower abdomen and some fever. He improved for a while, but while working in a lumber camp the intestinal trouble became so severe that he was obliged to discontinue his heavy work. In the fall of 1903 he was ill for three months again with "bowel trouble," with severe pain and constipation. Since then he has had difficulty in securing a daily movement. The fall of 1906 found the patient suffering much more pain all over the abdomen, but no diarrhea.

The present attack came on two weeks before admission to the clinic. He had suffered from diarrhea, after which his strength failed and he lost weight. There has been continual soreness and distress in his abdomen. He has had some slight nose-bleed of late. The severe headache has persisted for the past two days. The

patient has a tired expression. He protrudes his tongue, which is red, swollen, and heavily coated, very slowly. Breathing is accelerated and somewhat labored. Pulse small, low tension, regular rate 108, temperature 102. Percussion of the lungs was negative. A harsh vesicular breathing with râles could be heard all over the upper portion of the thorax. Heart not enlarged; sounds clear and of moderate intensity. The abdomen is below the level of the ribs; walls are moderately relaxed, and the spleen is just felt on deep breathing. There is some tenderness on palpation in the right iliac fossa. No rosella over trunk.

There was the suspicion of a more acute and recent infection. Examination of the urine gave a strong diazo reaction, and the following day the positive Widal assured us of the diagnosis of typhoid fever. The patient was given 5 grains of calomel, followed by salts. In the stools were found numerous trichomonads. The patient became more diarrheic as the typhoid fever progressed. Trichomonads were seldom seen in these frequent passages. At one time, however, many cyst forms were observed. No active parasites were present at this time, nor did they appear till three days later. Blood, due to the typhoid hemorrhage, was present on several occasions. Cholecystitis further complicated the course of the case.

At present the patient is well and about. His diarrhea abated with his convalescence. He still has two movements a day, as a rule. The feces are soft, light yellow in color, and contain a small number of trichomonads. He has not been constipated. The patient now states that he does not remember having been obliged to drink water that could have been considered stagnant or impure at any time previous to his first attack of pain and diarrhea.

CASE 5.—R. E. was referred from the surgical clinic for examination concerning pain in the right hypochondrium which spread over the entire abdomen. The patient was a male, aged 24, a day laborer by occupation. He had never had any previous illness. Three years previous he had an attack of "appendicitis." Following this the pain became constant. In the summer of 1905, appendectomy was performed at another hospital. The pain did not subside, however. At present he has aching and cramping pains in the right side which come on in the afternoon and last until midnight. They spread over the entire abdomen. Eating does not affect the pains. The patient vomits at times, but the vomitus has never looked black, nor has there ever been blood in the vomitus. No history of jaundice or clay-colored stools. No tarry stools. The patient has lost some weight. Heart and lungs are normal. Abdomen is below the level of the ribs. Spleen, liver, and kidneys not palpable. In a later examination, large peristaltic movements are seen in the epigastrium traveling from left to right. On distension of the stomach, no enlargement is noted. No pain. There is some pain and tenderness at the level of the eighth dorsal vertebra on the right side. At this time the patient was having on an average four stools a day.

Blood examination: 3,650,000 red cells, 7,000 white cells, 45 per cent. hemoglobin. Differential count shows no alteration in relative count.

Urine examination: Negative.

Test meals revealed a normal acidity, a lowered motility, an excess of mucus at times, normal amount of pepsin and chymosin. The stomach was neither enlarged nor prolapsed.

The stools on several examinations were pale brown in color and of creamy consistency. No undigested food remains. No blood. Occult blood test negative. Microscopically, large numbers of trichomonads were seen. They were very active and could be kept alive in the stool for ten hours at room temperature. No blood cells nor leucocytes seen. Four days after admission the morning passage gave a positive test for blood. Blood cells not seen.

As an exploratory operation was desired by the surgical clinic, the patient was put at rest, given a special diet, and Blaud's pills, in increasing doses, were administered. For the paroxysms of pain, morphin was given. The blood count improved considerably so that at the end of a week the red cells numbered 3,984,000, and the hemoglobin percentage was 70.

The patient had fewer passages, as was to be expected, but the stool was still soft and contained enormous numbers of trichomonads. An operation was deemed inadvisable at this time, and the patient, refusing to stay for further medical treatment, left the hospital. His subsequent course is not known.

CASE 6.—B. E. P. was admitted to the medical clinic Dec. 19, 1906, complaining of numbness, distress in the stomach and diarrhea. The family history is of value in one respect, in that a sister of the patient has pernicious anemia. He has been well up to the present illness, which began two years ago with loss of appetite, belching of gas and diarrhea. He vomited occasionally. In November, 1906, the numbness of which he now complains became pronounced. Ankles and feet especially felt cold; he lost both weight and strength. Recently his bowels have become constipated.

The patient is of slender build, musculature is soft and flabby. The skin is pale, dry and slightly inelastic. The tongue is furred, and the mucous membranes of the mouth are pale. Teeth are in good condition. Sclerotics are clear and of a bluish tinge. The lungs and heart are normal. The abdomen is two finger breadths below the level of the ribs. Slight tenderness in the epigastrium. Edge of the liver and the spleen can be felt on inspiration. Lymphatics not enlarged.

Blood: Red blood corpuscles, 2,464,000; leucocytes, 2,600; hemoglobin, 54 per cent. A differential count of 550 cells shows: Small lymphocytes, 42 per cent.; large lymphocytes, 16.5 per cent.; transitional, 5 per cent.; polynuclear, 40 per cent. There is much poikilocytosis; there are many megalocytes, but no megaloblasts are seen.

It is evident from the foregoing that this is another case of pernicious anemia.

About a week after the patient's admission, his bowels, which up to that time had been regular, and the feces normal and free from blood, became diarrheic. He had, at first, two partly formed passages which rose to five in a few days, and were liquid. They were yellowish brown in color, watery, and had a strong odor of hydrogen sulphid. There were a few undigested particles of meat and many starch granules. There was a small amount of mucus in fine flakes. In these particles many trichomonads were seen. No microscopic or occult blood.

The urine examination was as follows: Specific gravity, 1,025; acid reaction and reddish yellow in color. A 24-hour sample of 1,240 c.c. showed a large deposit of urates. Indican gave a deep blue reaction. No albumin; no sugar. A few fine granular short casts were seen.

The stomach examination showed an achylia, with a very rapid motility and an increase of mucus.

The patient was put on treatment for the pernicious anemia, and special attention was given to his diarrhea. The patient soon began to improve and his gain was rapid. The stools became natural and regular, and at the end of six weeks no more trichomonads were to be found. His blood picture has returned almost to normal, and at the last report the patient was enjoying good health.

CASE 7.—R. E. W., aged 31, is at present a student in the University. His family history and early history are of no importance in his case. He was a captain in the United States Marine Corps up to four years ago, and has been in all parts of the world, taking at that time no more than ordinary precautions about his food and drink. He first noticed his discomfort in the summer of 1903, while he was in Florida, where he drank from a spring the water of which he had

reason to believe was not absolutely pure. At that time the initial attack was characterized by pain in the abdomen, which began early in the morning and persisted all day. It grew worse toward noon, so that he could not be up and about. He felt better the next day. He did not vomit, had no fever and no diarrhea. The abdomen was sore for two or three days afterward. Every three months he has had similar attacks, which followed the same course. The patient says that just preceding the attacks he feels better than he has for some time before.

In the fall of 1905 he examined his stools for the first time and found *Trichocephalus dispar* ova and trichomonads in large numbers. I saw the feces soon afterward and was able to confirm these findings. I have studied the trichomonads in this patient's stools frequently, and always found them present in large numbers after the administration of a saline cathartic.

The patient later on took thymol and succeeded in ridding himself of the trichocephalus. Whether or not the trichomonads became fewer he does not know, but this drug must surely have had some effect on the organisms. He had the attacks with varying frequency up to January, 1906. He was often confined to his bed for a day or two, but at no time did he note any change in the consistency of his stools. Since the administration of thymol there have not been any very bad attacks. He had one last December which incapacitated him for one day.

On April, 8, 1907, he had the "beginning sensations" of another attack. The pain was less severe than on previous occasions, and he had no discomfort on the following day. It should be stated that during the first week in February the patient took ¼ gr. of calomel three times daily for one week.

A stool examined on April 11 showed a few trichomonads which had lively motion and all the characteristics previously noted. The number was greatly reduced to that which had been found on previous occasions on the giving of salts. No ova were seen.

The urine of the patient is normal in all respects, except for the occasional presence of indican.

Blood counts: Red blood corpuscles, 5,500,000; leucocytes, 8,000; hemoglobin, 80 per cent. The eosinophiles average at about 10 per cent., the proportion of the other cells being normal.

✓ Case 8.—The patient, male, aged 29, farmer by occupation, came to the hospital because of diarrhea, pain of a griping nature when the bowels moved, and extreme emaciation. He was admitted April 22, 1907. The family history and personal history up to first attack of diarrhea in 1900, are good. In December, 1900, the patient was employed as a surveyor, which required him to go to many different places and drink of waters that he has every reason now to think were unclean. At this time he first noticed a diarrhea, passing at the outset a few stools a day, and later having thin and watery passages about every two hours. He had no pain and lost no weight as he remembers. He recovered in two weeks so that he could return to his work. From this time on the patient had several attacks every year, each lasting for a variable length of time. Between the attacks the patient would gain considerably in weight only to lose this again in the next attack.

In March 1907, he had an attack of "grippe." No physician attended him, but soon after he was out of bed, he suffered a relapse accompanied by diarrhea. This has persisted since, and is the longest attack from which he suffered. The bowels were at first thin and watery, light yellow, and of a foul odor. At times they have been green. No blood and no dark stools. At times there has been a small amount of mucus. No food remains as far as he has noticed. He was never constipated between the attacks.

During the last thirty days the patient has lost thirty pounds in weight, he has grown very weak, and feels nauseated most of the time. In December 1906, he weighed 140 pounds. On admission his weight was 98 pounds. Temperature 98.8; pulse 82; respirations 20.

The thorax is markedly emaciated. The lungs are normal; the heart is not enlarged, nor are the sounds abnormal. The abdomen is slightly below the navel. Abdominal walls are thin. Peristaltic movements are seen in all parts of the abdomen, especially in the lower half. No localized rigidity and no pain points. Spleen, liver and kidneys are not palpable. No enlarged glands.

Stools:—Large, thin, watery, light-brown stool of foul odor; alkaline in reaction and containing a small amount of mucus. There was a faint occult blood reaction, but no blood seen on microscopic examination. A great many actively motile trichomonads were seen. No undigested food remains; a few pus cells; no crystals.

Stomach:—Test meals show an achlorhydria, apepsia and absence of rennin. Hypermotility marked. No blood; no leucocytes; no food remains; no excess of mucus; trace of lactic present on two occasions. On one examination of the fasting stomach a few actively motile trichomonads were seen. These have not been found since. A number of cocci and bacilli were present. A bit of stomach mucosa recovered from the lavage shows a mononuclear exudate. Round ulcer(?). No evidence of malignancy.

Blood:—Red blood cells, 2,490,000; white blood cells, 5,348; hemoglobin, 55 per cent.

Urine:—Normal.

The patient was confined to bed, given very soft diet, and an astringent. After the diarrhea was checked somewhat, he was returned to a more substantial diet and calomel in 1/10 grain tablets, administered every two hours, until eight were taken daily. He was kept on this for twelve days, at which time he began to have some slight loss of appetite and nausea. The calomel was stopped and the patient returned to intestinal diet, with a bitter stomachic before meals.

An examination of the stools at this time showed them to be entirely free from trichomonads.

The patient was now permitted to go out of doors, was given a fuller diet, and iron, in the form of Blaud's pills, was administered. He improved rapidly. On May 15, he had his first formed passage. It was free from organisms and blood. He has gained steadily in weight, and now weighs 118 pounds. He is still under observation.

CASE 9.—This patient, a male, student, aged 25, came to the out-patient clinic complaining of diarrhea. During the week of April 15-22, he had been out of town doing laborer's work and drinking of water that he believes was impure. On April 22 he first noticed that his stool was watery. The passages became more frequent at once, and continued in their watery character. The change came on suddenly. The bowels moved from 12 to 24 times daily. There was no griping nor pain at first, but lately there has been a little aching in the lower part of the abdomen with each defecation. The patient was given bismuth by his own physician with no relief. Later he was given a large dose of castor oil followed by salol and an astringment with no benefit. The diarrhea persisted, not quite so severe as before, but becoming worse at times. His appetite remained good. He lost some weight, and began to feel weak. He never noticed any blood, pus or food remains in the stools. They were lumpy at times and of foul odor.

The patient was a large well nourished man in good physical condition. Heart and lungs were normal. The abdomen was not tender to palpation and, except for a noticeable increased peristalsis, was negative. Rectal examination revealed a few hemorrhoids.

Stool:—Small, watery, yellow, of foul odor. Much undigested food present, mostly starch. Many red and white blood cells mixed in the small flakes of mucus. An enormous number of active trichomonads are seen.

Stomach:—Ordinary dinner removed in four hours; 150 c.c. recovered, acid and of sour odor; free hydrochloric acid, 50, total 84; no lactic acid; pepsin and rennin present. Microscopically, a few rods were seen. No trichomonads.

Blood:—Red blood cells, 4,200,000; white blood cells, 6,000; hemoglobin, 80 per cent.

Urine:—Normal in every respect.

On May 4, the patient was instructed to use a meat-free diet, and was given calomel in 1/10 grain doses, every two hours, till eight were taken. This was continued for one week, at the end of which time he was instructed to discontinue the calomel and observe the number of his daily passages. On the 12th he had three; on the 13th three; on the 14th two; on the 15th two; on the 16th three; on the 17th two. They all contained a few trichomonads, and were but partly formed. There was still some mucus, but no blood nor pus could be detected. The patient has been returned to his medication of calomel for another week and put on a more restricted diet. His blood has improved to normal, and he has regained his weight, feeling perfectly able to continue his work.

Case 10.—This patient was referred from the dermatological clinic, where he had been under treatment for urticaria, for treatment of his weakness and marked anemia. The patient is a civil war veteran, aged 62, and a farmer by occupation. He has had shortness of breath and weakness for many years, but for the past year this has been growing more pronounced. The patient gives a history of a severe diarrhea, alternating with constipation, dating from the civil war. During the war he states that he was confined to the hospital with typhoid fever, after which the diarrhea began and has given him more or less trouble ever since. At first, he would have an attack every two weeks, followed by a period of constipation. At these times he would have from 3 to 10 movements a day. The stools were of light color and contained a small amount of mucus, at times; no blood. Of late years the attacks have been growing less frequent, occurring about once a month, and lasting from 2 to 3 days. The passages are of the same character and just as numerous as before. The patient thinks that he can terminate an attack now by taking large doses of mandrake.

For the past year the patient has had some distress in his stomach after meals. He vomits occasionally, but the vomitus contained only food and mucus.

Blood examination:—Red blood cells, 4,000,000; white blood cells, 11,000; hemoglobin, 70 per cent.

Urine:—Normal.

Stool examination, after the administration of an ounce of Carlsbad salts: Large, yellow, sour, foul smelling, of amphoteric reaction. No food remains. Small amount of mucus. Many actively motile trichomonads and cercomonads seen. The former were in excess.

The patient could not stay for further treatment. He was given iron for the secondary anemia and advised to return.

In the foregoing series of cases the trichomonad is found under a variety of pathologic conditions. In some it strongly suggests itself as an etiologic factor; in others it plays a secondary part. That it is the cause of a chronic intestinal catarrh has long been held by many competent observers. Of late years, however, its influence in forms of enteritis has frequently been disputed. One reason for this has been that

we find the trichomonad living, at times, in necrotic areas, in pus and in the débris of growths. Here the trichomonad merely finds a suitable culture medium, as it is supposed to have, in the fecal material of cases of chronic diarrhea. Some observers cite instances to substantiate this view. But cases have been and are still being encountered where the intestinal conditions may be explained by the presence of these organisms. The fatal enteritis described by Galli-Valerio as occurring among guinea-pigs is proof of the fact that like parasites can cause a severe diarrhea in animals.* Furthermore, flagellate diarrhea, occurring in man, due to the *Megastoma entericum*, and infusoria diarrhea caused by the *Balantidium coli* and allied forms have been described.

There have been numerous reports in the last decade on all forms of flagellate enteritis. The work previous to that time has been classified and summed up by Janowski in an excellent manner. Notable among the series of cases that have been reviewed are those of Zunker, Grassi and Epstein. The former, in 1878, after making a systematic examination of all stools in Leyden's clinic, found nine cases of diarrhea without colic or tenesmus, in which flagellates were present. Nothnagel, soon afterward, met with the trichomonad in cases of acute and chronic catarrhal enteritis. He did not consider them harmful. Perroncito thought that a catarrh established itself through some other cause, and prepared a medium favorable for the development of the trichomonad. These organisms in their turn by irritating the epithelium assisted in maintaining the diarrhea. May, in 1892, found the trichomonad (*cercomonas coli hominis*) only in the small bowel, which was in a chronic catarrhal state. Roos made the trichomonad answerable for a persistent diarrhea. He believed that masses of them could set up a chronic irritation of the intestinal wall and cause increased peristalsis. Nothnagel's objection to this was that the bodies of these parasites were too soft to have any such effect. Grassi, though he had examined 100 cases of diarrhea in which trichomonads were found in the stool, could not make up his mind what part they played in causing such conditions. At least he did not attribute a specific action to them. Nor did von Jaksch, who found both cercomonads and trichomonads in severe enteritis of children, think they had any clinical significance.

Epstein, under the name of "Monocercomonas Diarrhea," described a severe form in 26 children. His report is an interesting as well as an important one and deserves mention in detail. There were 15 boys affected and 11 girls. He never found the condition in nursing children.

* I am aware of a similar epidemic that wiped out most of the guinea-pigs in a local laboratory one spring.

The youngest was 1 year old. Seven children were between 1 and 2 years of age; 11 between 2 and 3; 2 between 3 and 4; 1 between 4 and 5, and 4 were between 5 and 6. Children older than 6 were not examined. He thought that the diarrhea caused by these organisms was the same as any other diarrhea. At times, during the first few days of the infection, a slight rise of fever occurred. Pea-soup stools were the rule; blood was rare, and the reaction was alkaline. The course was either acute or chronic. In one case that came to autopsy no organisms were found in the jejunum; a few were seen in the ileum; many were present in the ascending colon; a very great number in the transverse colon; a few in the descending colon, and none in the rectum. At one time six children were taken ill together without any notable cause. The transmission apparently took place by water and occurred mostly in the dry seasons.

Epstein cited one instance where a weak, cachectic child was fed only special liquid diet; its stools were free from parasites. Three other children who had to drink tap water suddenly developed a diarrhea with these parasites in the feces. One day the weakling was given some tap water to drink, and quickly developed the same form of enteritis. The author could not find forms in the water. He finally concluded that these intestinal conditions and these trichomonads stand in direct relation to each other. They were not found in normal stools of children, and were present only where some such digestive and intestinal disturbances were complained of.

Boas, in 1896, described some additional cases. He did not feel certain whether the trichomonads caused the diarrhea or were merely a secondary infection.

Janowski reported six cases the same year, two of which argue strongly for the pathogenicity of the trichomonad. His second patient had persistent diarrhea, with colicky pain, for some time, failed gradually and finally died. The autopsy revealed in the ascending colon small ulcers of varying size, each covered with a layer of pus and mucus. The pathologic diagnosis was chronic dysentery. His fourth case was similar. A man of 35, complaining of acute dysenteric symptoms, had from three to four daily passages, which contained pus, mucus and numberless trichomonads. His pain and diarrhea persisted for four weeks, when death occurred. His colon also contained many small ulcers running as deep as the submucosa. There was round cell infiltration about the ulcer, and many eosinophiles were seen in some areas. The fifth patient in his series developed a sudden severe diarrhea four days before admission. A great many trichomonads were found in the first stool

examined. Calomel quickly checked the rapidly-increasing diarrhea, the patient recovering in a short time.

Janowski's conclusions were finally drawn from his six observations and from a consideration of the literature. He believed that the presence of the flagellates in the intestines was in most instances without any influence on the functions of the tract. It was only rarely that they instituted either a chronic enteritis or prolonged an old condition. These conclusions seem to be at variance with his experience as well as with his comments on Case 5 and the findings and diagnosis of Cases 2 and 4. It must be agreed that these two cases are different in many respects from any other known intestinal conditions.

Skaller, in 1898, commented on flagellate diarrhea after reporting a typical case in his experience. He found the trichomonads most numerous when the stools were the most frequent. He agreed with Nothnagel that they could not cause any more irritation of the intestinal wall than masses of casein would, but thought that in many cases they were merely associated with the diarrhea. In adults no cases have been reported in which they were undoubtedly the cause of the intestinal disturbance. Strube, the same year, reported the presence of flagellates in a woman suffering from an obstinate diarrhea and secondary anemia. Cohnheim, in 1901, exhibited several cases of infusoria diarrhea, one in a woman of 24, who had suffered with "mucous colic" for two years. He found that the administration of calomel caused a disappearance of the organisms together with the diarrhea. Japha, in discussing the subject, cited the case of a child who went from clinic to clinic complaining of periodic pains in the abdomen, loss of weight, diarrhea and marked emaciation. He found trichomonads in the stools. Following the administration of large doses of quinin and tannin, the child rapidly improved. Von Leyden and Uhlmann also reported cases in this discussion, both favoring the pathogenic action of the trichomonad.

Ucke, in 1903, contributed forty cases of flagellate enteritis, most of which were due to the trichomonad. He believed that they must have some action, in that they were so frequently associated with catarrhal enteritis. The stools had one common characteristic, in that mostly all were of a thin soupy consistency and alkaline. Westphalen, in discussing Ucke's report, did not think that the trichomonad was a rare intestinal parasite. He believed, however, that the number of trichomonads was proportionate to the severity of the diarrhea.

Rosenfeld considered the possibility of them causing a diarrhea at times. He did not believe they had a toxic action, because of the absence of eosinophilia. This argument I do not think can be accepted,

for the organisms may have a local action without causing any systemic disturbances. He added that another factor could usually be found, other than the trichomonad, as the specific cause of the diarrhea, and cited several instances in proof of this assertion. In one case of *Bothriocephalus latus* and trichomonad infection, both parasites were removed. Later the patient returned with achylia gastrica. In a second case of polyposis intestinæ, with diarrhea, the trichomonads appeared late, and only at several odd times in the course of the disease.

I might mention a similar instance in the cases reported by Osborne from this clinic where four different parasites were found in the feces, but these complications are usually misleading. In Rosenfeld's second case he does not state whether the advent of the trichomonad aggravated the condition or not. From his standpoint, then, the diagnosis of a flagellate diarrhea was no cause for alarm, but rather suggested that some other etiologic factor should be sought.

Terry, in 1905, added two important cases. The first patient, a man, had suffered for over twenty-two years. At first he had slight attacks of diarrhea. Later his passages became as frequent as twelve daily, with severe griping pains in the abdomen. The trichomonads were present in large numbers. One week after admission an exploratory laparotomy was done for supposed ulcer. None was found. The patient died of general peritonitis. Autopsy revealed some small areas in the cecum, 2x4 millimeters in diameter, pale, surrounded by a darker periphera, and covered with good mucous membrane. There was a slit-like ulcer, 4 millimeters long, and extending to the muscularis. It had a necrotic floor. All the large intestine showed small erosions from the ileocecal valve on, mostly in the cecum. They had a patchy, moth-eaten appearance, and seldom involved the submucosa. The second case was in a man who had periodic attacks of diarrhea, in whose stool trichomonads were always found. The patient had a clinical diagnosis also of pernicious anemia.

Emerson, in his recent work on clinical diagnosis, is the only author up to the present time who gives more than a word of description to these flagellates. He makes this statement: " . . . We could mention one or two cases in this connection in which this parasite seems to have been the cause of a severe diarrhea." Within the last year two observations of interesting cases have been published. The first to appear, that of Biland, occurred in a boy of 17, who had suffered for many years from a diarrhea, in whose stools enormous numbers of trichomonads were seen. After a prolonged illness the patient died, and a postmortem disclosed a diffuse, small-celled infiltration of the

mucosa of the small intestine. There were places where these cells were massed, but only in the upper layers of the submucosa. In the lower part of the ileum and in the colon were small, flat ulcers penetrating to the submucosa. They had a diphtheritic surface. Many eosinophiles, mast cells and plasma cells filled the surrounding tissue. The neighboring lymphatics presented the picture of a chronic lymphadenitis. Biland fixed the stained sections of the ulcers in series, and made smears of the surface, with the hope of finding the trichomonads. Of course, he failed in this, not because of the absence of the parasites or that they were unrecognizable, but because of the impossibility of preventing plasmolysis without proper precautions in fixation and staining. Though the intestinal tract had changes seen in leukemia, pseudo-leukemia and lymphosarcoma, the author believed that these intestinal alterations were due to an action of the trichomonad, which played, therefore, an important rôle in this case of enteritis. Krause reported a case of trichomonads associated with *Balantidium giganteum* in a typhoid fever stool. His patient recovered fully. He thought that there was more against than for the opinion that the trichomonad has a specific pathogenicity.

It would seem from a survey of the reported cases of intestinal trichomonad infection that a variety of conditions are produced by this organism. Truly, it has been found associated with many pathologic states. It has been met with in children, and in some adults, in severe forms of acute, and in chronic diarrheas, where no other etiologic factor was discoverable. That such a parasite should give rise to an enteritis in some cases and not in others is possible. We know that the organism thrives best in an alkaline medium. We know that the normal gastric acidity is destructive to the parasite as well as to the cysts. Surely, then, it must be that the organism reaches the intestine at a time when the hydrochloric acid is at a minimum, a fact that holds true for many pathogenic micro-organisms. Further, the intestine may not be wholly resistant to any action on the part of the trichomonad, be this mechanical or toxic. Or the patient may have already had a chronic catarrhal condition, forming thereby a suitable medium for rapid development of these parasites. None of these facts preclude the possibility of further destructive power on the part of the parasites. So, too, it may be that in some organic condition a secondary weakness on the part of the intestinal canal opens a way for infection by the trichomonad. That we have thus far been unable to explain just how the trichomonad infects or acts does not in the least signify that it can not be the cause of an enteritis.

It has long been known that the *Amebæ dysenteriæ* produces a typical ulcer and a definite form of enteritis, acute or chronic, with periods of convalescence and with exacerbations. It has been but a short while since we have had definite ideas how it produces necrosis and sloughing. We have not been able to produce diarrhea in animals with the trichomonad as has been done in the cat with the ameba. Perhaps we have been unable to find a way of transplanting the organism so that it will resist the destructive action of the stomach. We have seen a similar form, however, one which some observers hold to be identical with the *Trichomonas hominis*, cause a fatal diarrhea in guinea-pigs with nothing more than a marked hyperemia of the intestine and an occasional ulceration. Without the evidences of infection in adults, we have the work of Epstein showing how direct infection took place in a cachectic infant and the immediate results. Why not in other susceptible individuals?

Many of the cases that have been reported present so distinct a resemblance in symptomatology and pathology to each other and to some of the cases that I have outlined, that I believe it justifiable to group these conditions and specify them under the head of trichomoniasis, which may be either acute or chronic. If Epstein's work is to be accepted, and we have no reason to doubt its accuracy, then there is surely a distinct form of flagellate diarrhea occurring in childhood.

Let us note the similarity of cases in adults. In Case 1 of my series the pathologic findings correspond very closely to those reported by Janowski in his second and fourth cases; to Terry's fourth case and to Biland's. There was no eosinophile infiltration in my case at the sides of the submucosa. It may be that the progressive pernicious anemia from which the patient suffered accounted in part for their absence. Yet the frequency of these eosinophiles in other cases tends to show that there must be some local toxic action exerted by the trichomonad.

In adults the onset of an acute case is usually accompanied by severe abdominal pain, often colicky in character, radiating from side to side, and more or less constant. Nothing relieves it when at its height, except opiates. The stools are not necessarily frequent in these cases, but are usually increased in number, unformed or of fluid consistency. In Case 7, however, the patient never noticed any difference in their appearance, except after the use of cathartics. They are invariably alkaline and usually of a yellowish brown color. The trichomonads are present in enormous numbers, especially at the height of an attack, as, for instance, in Case 5, where I counted an average of eighty-two in a field, with a one-seventh Leitz objective No. 2 eyepiece. When convalescence sets in their number diminishes.

It might be argued that in each of my cases trichomonads were not found immediately after the onset of the symptoms. In chronic cases, however, each exacerbation was accompanied by an increase in the trichomonads in the stools. One interesting feature, and in this respect it resembles Terry's second case, is the fact that Cases 1 and 6 were clinically cases of pernicious anemia. Whether the diarrhea, which is a common symptom of pernicious anemia, existed previous to the trichomonad infection, or the flagellates caused the enteritis, which, followed by a secondary anemia, gradually developed into the pernicious type, would be difficult to determine.

Some writers claim to have found the trichomonad in normal feces. In Case 7 they existed in a stool of normal consistency, but there were symptoms in this instance undoubtedly due to the presence of these parasites. I have examined for them for four months at different seasons of the year in stools of patients that were given an ounce of Carlsbad salts on admission, and have never found them, except in cases where intestinal complaints were manifested. Furthermore, they have not been found in the routine examinations carried on in the medical clinic in other intestinal cases.

There is no doubt about the efficacy of calomel in destroying the trichomonad. In fact, it is usually found that after the administration of small, repeated doses, the diarrhea diminishes, the pain ceases and the patient rapidly recovers. Other drugs, such as quinin, tannin, salol, thymol, naphtholen and beta-naphthol, have been employed at times with some success.

With our limited knowledge of the reproduction and cultural characteristics of the trichomonad the method of entrance into the intestinal tract can not readily be determined. The most likely way is through food and drink, whereby the spores are ingested. The small intestine is frequently the seat of these organisms, as can be shown by irrigating the colon and giving a saline cathartic; then examining the feces for active forms, before and after, in both instances. The commonest seat is the large intestine from the cecum to the sigmoid colon. It is in the ascending and the transverse portions of the colon that the ulcers are usually met with and most of the round cell infiltration occurs.

It is not my intention to speculate on the manner in which the trichomonad brings about these intestinal changes. The mechanical theory is not a likely one. That the trichomonad produces a toxin is plausible. To presume that this toxin is a secretion, or the result of the activity of the organisms on the intestinal contents, would not be justified. Withal, I firmly believe that the trichomonad is the direct cause of certain forms

of acute, chronic and recurring enteritis, characterized by abdominal pain, diarrhea, loss of weight and strength, with slight temperature at times, and anemia. Whatever may be the immediate result of its introduction into the intestinal tract, this fact remains, that its removal or a great reduction in the number of organisms present usually results in a marked lessening of symptoms or a complete recovery.

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68. Tham: Virchow's Arch., 1870, i, 314.

69. Theobald: Centrlbl. f. Bakteriologie, 1904, p. 86.

70. Ucke: St. Petersburger med. Wochschr., Feb. 10, 1903, p. 294, Mikrobiologische Gesellschaft zu Petersburg, February, 1904, Beobachtungen über Flagellaten in Feces des Menschen.

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72. Zabel: Arch. f. Verdauungsk., 1901, vii, 509. Megastoma intestinalis und andere Parasiten in den Zotten eines Magenkrebses.

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AN EXPERIMENTAL STUDY OF THE ACTION OF OIL ON GASTRIC ACIDITY AND MOTILITY.

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This investigation was commenced with the idea of perfecting a method of experimentation on the human stomach which has been employed more or less systematically in the medical clinic of the University Hospital for a number of years.[1] Much of the knowledge concerning the action of the various drugs and remedies administered in the treatment of stomach disorders has been deduced from the results of purely empirical procedures. In recent years, however, quite a number of scientific experiments have been conducted, particularly in Europe, which furnish the profession much useful information concerning food reactions in the stomach. Some of the methods employed to solve certain problems regarding digestion are fairly accurate, while others are subject to more or less criticism; consequently the chief aim of this study has been to overcome these defects in so far as possible. Notwithstanding the difficulties of this task, it seemed possible that by paralleling Pawlow's classic experiments on dogs one might obtain evidence justifying the conclusion that all reactions obtained by experimentation on canines with miniature stomachs occur to a greater or less extent in man.

The authors had been employing olive oil as a routine treatment for hyperchlorhydria in all its forms, both in hospital and private practice, for a number of years, with such favorable results that the desirability of determining its effects on the gastric functions experimentally prompted the present investigation herewith reported. Results of clinical observations, which are not based on technical experimentation, have revealed many indisputable truths concerning digestion, but the science of medicine will be advanced greatly if these observations can be confirmed and the action of drugs demonstrated by actual experiment.

It is an ancient idea that fats retard digestion. Aristotle evidently observed phenomena of this nature before expressing the opinion: "Now the best digestion is in the bottom of the stomach, because the fat

1. Cowie: Physician and Surgeon, Detroit and Ann Arbor, 1903, xxv, 241-252.

descends not there; such as eat fat meat are very sleepy, by reason that digestion is hindered." Pawlow[2] has aptly said that "physiology stood for a long time in sharp conflict with practical medicine. Physicians bringing forward their observations in proof had long answered the question in the affirmative. . . .

"Physiologists, on the other hand, had fruitlessly endeavored, for decades, to arrive at definite results." Dr. Chigin,[2] working in Pawlow's laboratory, demonstrated that fat and starch have no exciting effect on the glands of the dog's stomach. Pawlow devoted particular attention to the investigation of vegetable and animal fats. "They were tested not alone on a dog with an isolated miniature stomach, but also on animals with gastric and esophageal fistulæ, and finally on dogs which had survived the operation of separation of the vagi in the neck, performed several months previously." In all cases the fat was directly introduced into the stomach without swallowing. The results were negative.

When this experimenter poured 100 c.c. of oil into the main stomach of a dog by means of a "sound," and one-half to one hour later the dog was given 400 grams of flesh, instead of the usual five to ten minutes, half an hour elapsed before the beginning of secretion, and when it commenced it was scanty, only three to five c.c. being collected in from two to three hours, while under other conditions ten to fifteen c.c. were secreted in the same time. When the oil was introduced into the stomach immediately after eating the meat, "the secretion began with normal energy, and only later did the inhibitory influence make its appearance." "The same results were obtained when the dog was given fat mixed with meat." A lowering of the digestive function as well as the amount of juice was noticed.

Pawlow concludes that "fat depresses, that is, inhibits the normal energy of the secretory process," and is forced to the further conclusion that this inhibition is central, by reflex stimulation of the inhibitory nerves of the glands, or the inhibitory centers of these nerves, and not to the mere mechanical effect of covering over the mucous membrane and preventing excitation of the nerve endings.

Backman,[3] in his investigation, first washed the fasting stomach with warm water, after which he administered daily alternations of fat and fat-free food. Samples were obtained by expression, at intervals of one-quarter to one-half hour, until the stomach was empty, which was proved subsequently by washing. Similar investigations with and with-

2. Pawlow: The Work of the Digestive Glands, lecture, translated by W. H. Thompson, London, 1903, 80.

3. Backman: Ztschr. f. klin. Med., 1900, xl, 224.

out the fat were usually conducted two or three times with the same meal. Unfiltered contents were used for the determination of the acids. The meals employed were the following:

I. French bread .....100 grams.
Butter ..... 50 grams.
Water .....300 grams.

II. French bread .....100 grams.
Cream .....300 grams.

III. Oatmeal porridge, made of 6 grams of oatmeal, steamed with enough water to make 357 grams. To this 50 to 199 grams of butter were added during the cooking.

From his investigations Backman concluded that HCl was decreased from 2 to 42 per cent. by the employment of fat, these figures being obtained with the cream meal. He also found that butter delayed the appearance of free HCl in one of his cases, and that cream delayed it in two cases out of three. The rise of the acidity curve, which is slower with fat than without, often lasts until the end of digestion, exhibiting marked contrast with the control meals, in which the highest values for free HCl are in the middle of the digestion period. In other words, there is a decline in the secretion of the gastric juice and a lengthening of the time of digestion when oil or fat is ingested with the meal.

Strauss and Aldor[4] report experiments on seven cases of hyperchlorhydria. Their purpose was to determine the effects of the substitution for carbohydrates of fat given in abundance, but in quantities not so large as to cause discomfort of the patient or to interfere with the assimilation of fat. They employed three sets of meals:

I. Control meal, consisting of one roll and 300 c.c. of tea. This was allowed to remain in the stomach one hour.

II. Gum arabic meal, consisting of one roll, 300 c.c. of tea, and 5 grams of gum arabic.

III. Oil meal, consisting of one roll, 300 c.c. of tea, 5 grams of gum arabic, and 30 grams of oil of sweet almonds.

IV. Olive oil meal, consisting of one roll, 300 c.c. of tea, 5 grams of gum arabic, and 60 grams of olive oil.

Seven cases in all are reported. All the cases, except 2 and 5, received two control meals. Cases 3 and 4 received one initial meal and one gum meal as control. In five of the cases there was a diminution in the values of the acids as contrasted with the controls. This was marked in Cases 1, 3 and 4. Cases 2, 3, 4 and 7 show variations which are certainly not marked, except in Case 3, where, after the gum meal, the HCl value rose from 8, with the previous meal, to 35, and fell to 10 and 6

4. Strauss and Aldor: Ztschr. f. Diätet. u. physik. Therap., Leipz., 1898, i, 117.

with the oil of sweet almond meal. The increase from 8 to 35, the authors assert, is due to the action of the gum arabic, which had a similar action in nearly all of the cases. So far as this part of their work is concerned, Strauss and Aldor reach the conclusion that oil depresses the secretion of acid. It would seem that their cases were not sufficiently controlled nor sufficient in number to justify very definite conclusions.

Ewald and Boas[5] employed a test meal consisting of 1 to 2 per cent. starch paste and pure neutral olive oil in the proportion of four to one. They conclude that after the administration of a mixture of paste and oil, as contrasted with paste alone, no free HCl appears during the first half-hour.

Akimow-Peretz[6] investigated the effect of the daily administration of almond oil over long periods. Fifty to 100 c.c. were given before eating. A lowering of the acidities in 16 out of 18 cases was found. An emulsion of almonds made by grinding up a tablespoonful of sweet almonds into a meal, and adding boiled water, so that the amount of the strained fluid, after thoroughly shaking, equaled about 300 c.c., gave similar, but not so marked, results.

ORDER OF AUTHORS' INVESTIGATION.

1. The patient was chosen with much care. He was one who had first become thoroughly familiar with the manipulations of the stomach tube, that is, he could swallow it without discomfort or retching, was able to retain it for an indefinite period of time, and to prevent the saliva from entering the stomach in any undue amount. The cases studied at the University Hospital were admitted for stomach complaints. Those patients examined at the Craig Colony presumably had normal stomachs; at least none of them complained of gastric symptoms.

2. A uniform test meal was employed in each case so that the food stimulation would not vary from day to day. It was given at approximately the same time each day and was removed from the stomach at a definite time after eating. The patients studied at the University Hospital were given a shredded wheat biscuit, which has a fairly constant weight of 30 grams, and, after eating this dry, 300 c.c. of water. At the Craig Colony, 30 grams of very dry toast, with at first 400 c.c. and later 300 c.c. of water, were given. Olive oil was used almost exclusively at the University Hospital. Cotton seed oil was given preference at the Craig Colony, olive oil being used only a few times.

3. After the secretion range was established by a series of meals the

5. Ewald and Boas: Arch. f. path. Anat. (etc.), Berl., 1886, civ, 271.
6. Akimow-Peretz: Abstract, Arch. f. Verdauungskr., Berl., 1898, iv, 397.

oil was given at a definite time in relation to the meal and the examinations conducted in the same way as with the controls until a sufficient number were obtained. If the patients remained in hospital long enough, the oil was withdrawn and the tests continued.

4. Two series of experiments were conducted in every case, one as described above, where the contents were recovered one hour after ingestion, and the other by what is designated the special meal series, in which samples were removed from the stomach at frequent intervals, 5, 10 or 15 minutes, until the stomach was empty. A final lavage was given to assure the removal of all food from the stomach; a definite amount of water was employed. The reactions of the fluid obtained after the lavage were also tested. In the beginning of the investigation, the tube was allowed to remain in the stomach during the entire stage of digestion. Later the tube was removed after each sample was obtained.

5. The chemical analyses consisted in the estimation of free HCl with di-methyl-amido-azo benzol as indicator; of the total acidity with phenolphthalein as indicator; of peptic strength by Mett's method.[7] To eliminate the personal equation, each case was studied by the same person. This rule was rarely broken. However, we had determined by testing ourselves that we read to the same end reaction.

By adhering as closely as possible to these procedures and by examining a sufficient number of cases, we have hoped to eliminate many factors of error which must necessarily exist in an investigation of this nature.

The effect of oil was investigated on three definite functions of the stomach—on the rate and height of secretion and on the drainage or motor power of the stomach. Final conclusions concerning each of these are based on comparisons of the average results of large numbers of meals with and without oil administered in definite relation to the meal.

ILLUSTRATIONS OF THE IMPORTANCE OF CARE IN THE SELECTION OF SUITABLE CASES FOR EXPERIMENTATION.

The following cases are only a few of the many that can be given from the clinical records of the University Hospital illustrative of how useless any investigation would be without first having controlled the range of secretion by keeping the subject under the same conditions from day to day. It was pointed out many years ago by Ewald, in the first edition of his Klinik der Verdauungskrankheiten (1888), that there is often a daily difference of from 20 to 27 degrees of acidity in

7. Cowie: Physician and Surgeon, Detroit and Ann Arbor, 1904, xxvi, 118-121.

the normal stomach. From a perusal of the literature it would seem that this fact had not been much considered.

CASE 1.—Louis M.

	Free HCl.	Total acid.
Dec. 16, 1904	26	42
Dec. 17	0	16
Dec. 18	0	12
Dec. 19	10	28
Dec. 20	22	40
Dec. 21	30	46
Dec. 22	34	52

Stimulus equivalent to an Ewald test breakfast.

CASE 2.—Miss A. K.

	Free HCl.	Total acid.
Feb. 23, 1905	28	28
Feb. 24	40	48
Feb. 25	48	60

CASE 3.—Mr. B.

	Free HCl.	Total acid.
Oct. 4, 1904	0	4
Oct. 5	0	15
Oct. 7	0	15
Oct. 8	0	12
Oct. 26	0	10
Oct. 27	0	20
Oct. 28	10	35
Nov. 7	0	50
Nov. 15	10	30
Nov. 16	8	26
Feb. 22, 1905	0	30
Feb. 24	0	28
Feb. 25	0	14

CASE 4.—A young man with hyperacidity. The fasting stomach showed, on March 24, the presence of HCl and pepsin. After a shredded wheat biscuit meal, samples were taken every fifteen minutes. The first apearance of HCl (Günzburg) was noted at 52 minutes. The highest HCl value, 42, was obtained at 67 minutes. The stomach was empty at 112 minutes, and the total amount recovered during this time was 151 c.c. The following day, March 25, the fasting stomach was empty. Two ounces of cotton seed oil were given one-half hour preceding the shredded wheat biscuit meal. The first appearance of free HCl was at 69 minutes. The highest free HCl value, 31, was obtained at 129 minutes. The stomach was empty at 159 minutes, and the total amount recovered during this time was 218 c.c. April 1, two ounces of cotton seed oil were given, as before. There was no HCl secreted during the hour. April 2, no oil preceded the biscuit meal, and no HCl was secreted.

In Cases 1 and 3 one could easily choose three successive meals which might suggest a condition directly opposite to that which was dominant. Case 4 shows how incomplete work might have given an apparent basis for very definite conclusions as to the action of olive oil. Had the fourth meal not been given, the conclusion might have been reached that an excellent demonstration of the depressant action of oil on the acidity had been obtained. The fourth meal, however, obviates any such conclusion and shows that the secretion in this case was disturbed by nervous influences.

SERIES 1.—The following are the cases studied at the University Hospital:

CASE 5.—Mr. F. This patient had a distinct chemical hyperchlorhydria without subjective symptoms, excepting constipation. He had attacks of nocturnal unconsciousness, accompanied by vomiting and frothing at the mouth, followed by pain in the stomach and soreness of the abdominal muscles. No attacks during investigation.

Chart 1, Case 5.—Mr. F. Record of daily meals. Total acid indicated by upper (heavier) solid line. Free acid indicated by lower solid line. Average total acidity indicated by upper dotted line. Average HCl indicated by lower dotted line.

EXPERIMENT 1.

Date.	Quantity.	Free HCl.	Total acid.	
Sept. 30	30 c.c.	27 c.c.	40 c.c.	Control.
Oct. 1	35	7	19	Control.
Oct. 2	160	54	66	Control.
Oct. 6	120	49	63	Control.
Oct. 7	15	50	70	Control.
Oct. 8	10	20	32	Control.
Oct. 9	10	50	65	Control.
Oct. 10	40	62	76	Control.
Oct. 11	40	52	64	Control.
Oct. 12	7	40	50	Control.
Oct. 13	..	40	50	Control.
Oct. 14	0	..	..	Control.
Oct. 15	75	76	88	Control.
Oct. 16	75	72	84	Control.
Oct. 17	25	57	80	Control.
Oct. 18	..	51	70	Control.
Oct. 19	75	62	80	Oil, 1 oz. after.
Oct. 20	50	52	69	Oil, 1 oz. after.
Oct. 21	30	54	70	Oil, 1 oz. after.
Oct. 22	172	24	34	Oil, 1 oz. after.
Oct. 23	48	55	70	Oil, 1 oz. after.
Oct. 24	40	55	75	Oil, 1 oz. after.
Oct. 25	110	60	82	Oil, 1 oz. after.
Oct. 26	75	58	72	Oil, 1 oz. after.

Date.	Quantity.	Free HCl.	Total acid.	
Oct. 27	175	4	16	Oil before.
Oct. 28	180	10	20	Oil before.
Oct. 29	208	12	28	Oil before.
Oct. 30	..	15	25	Oil before.
Oct. 31	5	0	10	Fasting stomach.
Nov. 1	150	60	78	Oil after.
Nov. 2	115	45	57	Oil before.
Nov. 3	254	17	28	Oil before.
Nov. 4	210	32	42	Oil before.
Nov. 5	228	18	28	Oil before.
Nov. 6	60	40	65	Oil before.
Nov. 7	Special meal.			
Nov. 8	Special meal.			
Nov. 9	Special meal.			

EXPERIMENT 2.

CASE 5.—Mr. F. Control meal. XI-9-1903.

Time.	Amount.	Free HCl.	Total acid.	Pepsin.	Pepsinogen.
6:35	Began eating.				
6:42	Finished eating.				
6:45	10 c.c.	0 c.c.	0 c.c.	0 c.c.	3.61 c.c.
6:50	11	0	0	0	6.7
6:55	9.5	4	10	0.36	13.6
7:00	12	10	21	2.56	
7:05	11	19	32	4	
7:10	10	21	40	9	
7:15	10.5	20	40		
7:20	10	25	50	6.7	
7:25	10	30	56	9	
7:30	11	40	60	12.2	
7:35	10	40	62	10.9	
7:40	9.5	48	68	15.2	
7:46	10	40	68	16	
7:50	10	30	52	11.2	
7:55	5	28	50	9.61	
8:00	Lavage.	Practically clear.		Free HCl, 11 c.c.	

Meal with oil immediately before eating. XI-7-1903.

8:10	Began eating.				
8:17	Finished eating.				
8:20	10 c.c.	0 c.c.	0 c.c.	..	2.89 c.c.
8:25	11	0	7	..	2.56
8:30	10	0	0	..	1.4
8:35	13	0	7.5	..	2.56
8:40	11	10	20	..	3.24
8:45	10	10	20	..	4
8:50	10	0	10	..	....
8:55	11.5	18	30	..	3.24
9:00	8	16	28	..	4.41
9:05	11.5	16	30	1.96	
9:10	10.5	20	29	..	
9:15	10	19	28	6.76	
9:20	10	40	57	9	
9:25	10	40	50	10.9	
9:30	10	30	46	9	
9:35	10	32	42	4	
9:40	5	33	45	9	

Lavage clean. Free HCl, 10 c.c.

In Charts 2, 3, 7, 8, 9, 10 and 11 the figures at the top in minutes represent the time subsequent to the beginning of eating.

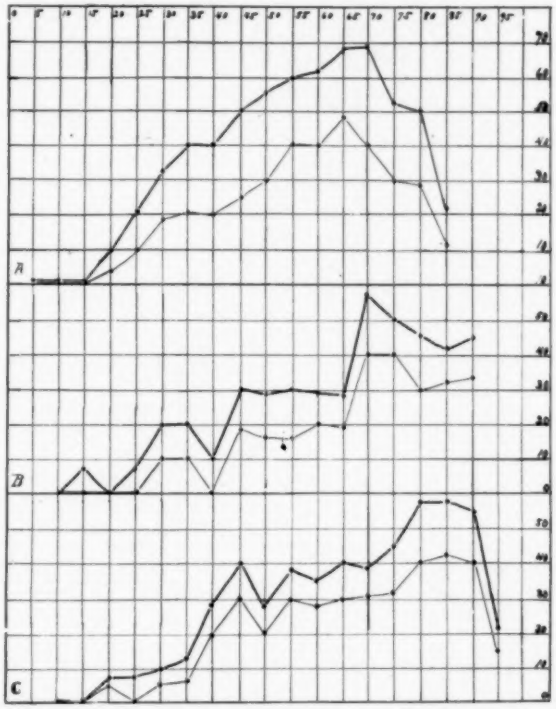

Chart 2, Case 5.—A, control. B, olive oil immediately preceding the meal. C, olive oil immediately after the meal.

Case 5.—Mr. F. Oil immediately after meal. XI-8-1903.

Time.	Amount.	Free HCl.	Total acid.	Pepsin.	Pepsinogen.
8:15	Began eating.				
8:23	Finished eating.				
8:25	10 c.c.	0 c.c.	0 c.c.	..	15.3 c.c.
8:30	10.5	0	0	..	12.9
8:35	10	5	7	..	14.4
8:40	10	0	7	..	8.4
8:45	10	5	10	0	
8:50	10	26	13	..	
8:55	10	20	28	10.5	
9:00	10	30	40	24	
9:05	10	20	28	13.4	
9:10	10	30	38	18.5	
9:15	10	28	35	27	
9:20	10	30	40	22	
9:25	11	31	38	18.5	

Time.	Quantity.	Free HCl.	Total acid.	Pepsin.	Pepsinogen.
9:30	10	32	46	19.4	
9:35	10	40	57	18.5	
9:40	10	43	57	20	
9:45	8	40	55	23	
9:50	*Lavage about clean. HCl, 15 c.c.				

*Order of investigation.

From a study of these tables and the accompanying charts the following deductions can be made:

1. In the daily meals, Table 1, the oil was given in close relation to the meal. When it was given immediately after the meal, there was practically no change in the acid values over those of the control meals, but the progress of digestion was somewhat delayed. When the oil immediately preceded the meal, a decided decrease in the amount of the free acid was noticed. On November 1 a mistake was made and the oil given immediately after the meal, and the same result was obtained as in the previous administration of oil at this time. However, on November 2 and 6 a somewhat similar comparative lack of depression occurred when oil was administered before the meal.

2. The special meals show that the appearance of free HCl is distinctly delayed when oil is given before the meal, but is unaffected when oil is given after the meal. The height of secretion is greatest when oil is not used; it is apparently slightly lowered when oil is given either before or after the meal, and is distinctly delayed when oil is given after the meal.

3. The rate of increase in the quantity of free HCl is delayed by oil before or after the meal; this delay is more marked when oil is given before the meal. The curve of the rise of the acidity may be said to be concave with oil and convex without oil. Taking the readings one hour after each of the special meals, the free HCl is distinctly lower where oil was administered before the meal than after meals without oil; when oil was given after the meal it is only slightly lower, corresponding closely with the results obtained in the daily meals. The case did not remain long enough to enable any conclusions as to the permanency of the effect of the oil treatment. This will be discussed later.

4. Variations in the amount of HCl observed may be due not to the lessened secretion, but to the retarded secretion. In the special meals the secretion often rises as high, but the rise is markedly delayed by the oil, and at the end of the usual time at which a test meal is removed from the stomach the acid value is distinctly lowered.

CASE 6.—Mr. J. Peptic ulcer; subacute; hypersecretion; robust railroad conductor; symptoms of hyperchlorhydria marked. Operation, gastroenterostomy; recently active ulcer; recovery complete.

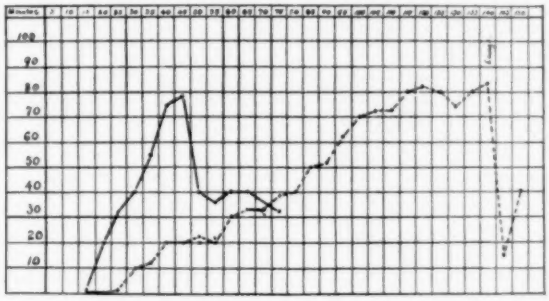

Chart 3, Case 6.—Mr. J. Experiment 1, control meal indicated by solid line. Olive oil meal indicated by dotted line.

EXPERIMENT 1A.—MR. J., SHREDDED WHEAT BISCUIT MEAL WITHOUT OIL.

Time.	Quantity.	Free HCl.	Total acid.	Peptic value.	Lugol reaction.	Remarks.
7:55 a. m.....	After lavage began eating.					
8:00.....	Finished eating.					
8:03.....	11 c.c.	03 c.c.	12 c.c.	0.00 c.c.	B V	
8:08.....	10	20	30	10.24	V B	
8:13.....	10	33	43	20.25	V B	
8:18.....	10.5	40	53	16.00	V B	
8:23.....	10	55	70	12.25	V B	
8:30.....	10.5	75	90	14.44	V B	
8:31.....	8.5	78	98	6.25	V B	
8:47.....	11	40	52	7.84	A C	Viscid.
9:03.....	11	37	50	6.76	A C	More viscid.
9:18.....	11	40	57	23.04	A C	Very viscid.
9:28.....	10.5	40	60	9.00	A C	Less viscid.
9:30.....	5	..	..	.....	...	
9:40.....	9	32	42	14.44	A C	
9:48.....	Stomach washed. No HCl in washings.					
9:53.....	Tube passed, aspiration continued for three minutes., 1 c.c. viscid fluid. No reaction for HCl.					

CASE 6.—Mr. J.

EXPERIMENT 1B.—MR. J., SHREDDED WHEAT BISCUIT MEAL PRECEDED BY OIL.

Time.	Quantity.	Free HCl.	Total acid.	Peptic value.	Lugol reaction.
8:10½.....	After lavage 50 c.c. of olive oil was taken.				
8:12¼.....	Began eating the test meal.				
8:20.....	Finished eating.				
8:26.....	10.5 c.c.	0 c.c.	? c.c.	0	B
8:31.....	11.0	0	10	0	V B
8:36.....	12.75	..	15	0	V B
8:41.....	10.0	10	20	0	V B
8:46.....	10.0	12	22	2.25	V B
8:51.....	10.0	20	30	2.89	V B
8:56.....	10.0	20	30	6.25	B V

Time.	Quantity.	Free HCl.	Total acid.	Peptic value.	Lugol reaction.
9:01	10.0	22	33	6.25	B V
9:06	10.0	20	30	10.8	B V
9:11	10.0	30	40	5.29	B V
9:16	10.0	33	45	7.84	B V
9:21	11.0	33	44	5.29	V B
9:26	10.0	38	48	7.84	B V
9:31	10.0	40	55	10.8	V B
9:36	10.0	50	62	10.8	B V
9:41	11.0	53	70	16.8	B V
9:46	11.0	62	78	7.84	BB V
9:51	10.0	70	85	7.29	B V
9:56	10.0	73	90	10.8	VV B
10:01	10.0	73	88	10.8	VV B
10:06	10.0	80	92	12.25	VVV B
10:11	10.0	82	96	10.08	VVV B
10:16	10.0	80	100	7.29	VV B
10:21	10.0	76	90	18.49	B
10:26	10.0	80	95	22.09	A C
10:31	20.0	83	100	28.09	A C
10:31	Stomach washed, water returns clear dimethyl-amidoazobenzole.				
10:36	11 *	15	30	10.8	B V
10:41	5.5	40	50	8.6	B V

Lavage after last sample contained no free HCl.

*Few flecks of meal.

CASE 6.—Mr. J.

EXPERIMENT 2.—ORDINARY DAILY SHREDDED WHEAT BISCUIT MEALS, OIL AS SPECIFIED.

Date.	Quantity.	Free HCl.	Total acid.	
April 9	76 c.c.	62 c.c.	72 c.c.	Control.
April 10	120	78	88	Control.
April 11	120	66	74	Control.
April 12	120	70	88	Control.
April 13	75	52	60	Control.
April 14	65	50	59	Control.
April 15	60	52	62	Control.
April 16	55	88	81	Control.
April 17	280	22	34	Oil before.
April 18	130	38.6	54	Oil before.
April 19	173	10	26	Oil before.
April 20	195	44	60	Oil before.
April 21	220	14	30	Oil before.
Average	74	62.5	73	8 without.
Average	199.6	25.7	41	5 with.

In this case a most pronounced change is seen in the rate and height of secretion, as well as in the motor power. With the special meal there is a distinct lengthening of the digestive period. Digestion, instead of continuing one hour and forty minutes, as it did in the control meal, was lengthened to two hours and ten minutes when the meal was preceded half an hour by oil. In the oil meal the rate of secretion of hydrochloric acid was markedly retarded. With the control meal a free acid value of three was obtained 12 minutes after beginning to eat; with the

oil meal 23½ minutes elapsed before the faintest reaction for free acid could be demonstrated.

The height of digestion, 78, with the control meal was reached in the middle of the digestive period, 40 minutes after beginning to eat, while with the oil meal the height, 82 to 83, was attained at the end of the

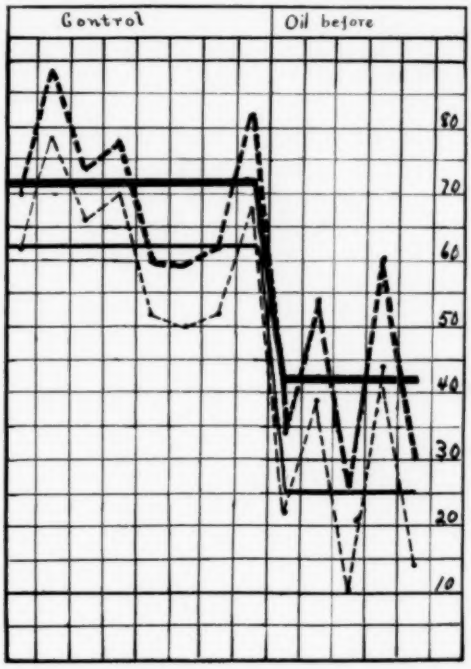

Chart 4, Case 6.—Mr. J. Daily meals. The upper and heavier dashed line is the total acidity curve, which is averaged in the solid, heavier line; similarly, the HCl is shown in the lower dashed line and this is reduced to average in the lower solid line.

digestive period, about two hours after beginning to eat. The total output of HCl has, by this time, reached a quantity considerably above that observed in the control meal.

The motor power is distinctly lowered by the oil. With the control 128 c.c. were recovered during the stage of digestion; with the oil meal over twice as much, 277 c.c., were obtained. At the end of one hour, the usual time a test breakfast is permitted to remain in the stomach, the

secretion with the control meal is slightly in advance of that in the oil meal.

With the peptic values there is a change corresponding in each meal with the change in the acids.

Doubtless little reliance can be placed on Lugol's test for starch digestion in an experiment of this character. It would be reasonable to expect that, with 23 minutes of practically achlorhydria, much, if not nearly all, of the starch would have undergone the change to anachrom. With the oil meal anachrom was not obtained until the end of digestion, when the free acid was excessively high. The erythrodextrin stage was quickly reached in each case. For this reason the tests were not continued in the other cases.

The daily meals show similar effects from the oil. The height of the secretion is, however, more markedly lowered with the oil meals. The decrease in motor power in the oil meals is as striking as it is in the special meal, the average amount recovered being nearly three times as much as the control. This rather tends to strengthen the value of the special meal, which, together with the daily meals, may be said to be fairly representative of what actually takes place in this case after oil is administered.

CASE 7.—Mr. N. Stomach neurosis.

Date.	Amount.	Free HCl.	Total acid.	Peptic value.	Remarks.
October 27, 1903...	100 c.c.	32 c.c.	70 c.c.	4.84	Control meal.
October 28.....	74	55	75	4.41	Control meal.
October 29.....	75	52	66	12.25	Control meal.
October 30.....	96	50	64	16.00	Control meal.
October 31.....	74	49	64	5.29	Control meal.
November 1.....	..	52	64	4.84	Control meal.
November 2.....	25	45	60	10.24	Control meal.
November 3.....	60	52	67	4.90	Control meal.
November 4.....	80	54	66	4.41	Control meal.
November 5.....	90	26	42	1.60	Oil given ½ hr. before.
November 6.....	50	50	62	5.10	Oil given ½ hr. before.
November 7.....	300	0	11	0.00	Oil given ½ hr. before.
November 8.....	199	58	78	2.60	Oil given ½ hr. before.
November 9.....	120	56	70	20.50	Oil given ½ hr. before.
November 10.....	65	39	59	3.01	Oil given ½ hr. before.
November 11.....	70	60	75	16.00	Oil given ½ hr. before.
November 12.....	92	66	80	21.78	Oil given ½ hr. before.
November 13.....	102	32	42	3.02	Oil given ½ hr. before.
November 14.....	70	52	66	9.93	Oil given ½ hr. before.
November 15.....	62	38	57	9.27	Oil given ½ hr. before.
November 16.....	70	54	69	1.06	Oil given ½ hr. before.
November 17.....	152	0	13	0.00	Oil given ½ hr. before.
November 19.....	71	60	70	.....	Oil given ½ hr. before.
November 20.....	118	8	22	0.28	Oil given ½ hr. before.
November 21.....	68	48	64	14.06	Oil given ½ hr. before.

In this case no special meals were given. The acidity curve for the nine days preceding the oil meals was comparatively constant. The fluctuations were within fairly narrow limits. As soon as the oil is given, wide variations are noted. At one time, November 7, there was no secretion of free acid, and the total acidity was only 11; the motility was also markedly lowered, 300 c.c. being recovered at the end of one hour. After this the fluctuations continued within wide limits, touching zero again in ten days, but with a less marked lowering of the motility. On the twentieth day the HCl dropped to 8, but the same stimulus gave an acidity of 48 on the following day.

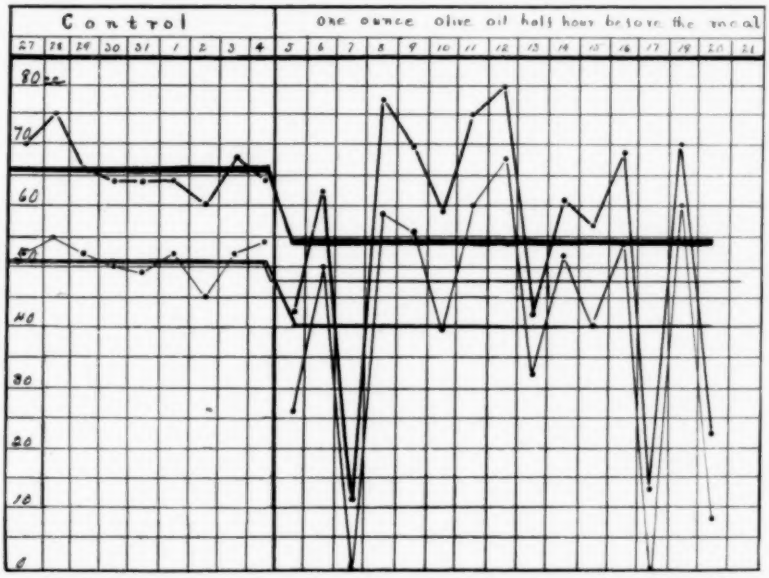

Chart 5, Case 7.—Daily meals. The upper broken line is the total acidity curve, which is averaged in the upper continuous line. The HCl is shown in the lower broken line, and reduced to average in the lower continuous line.

If a curve of the average for the control and the oil meals be plotted, a distinct depressant effect from the oil is noted. In the presence of two 0 and one 8 acid values that can not be explained, it is a question whether the average lines should be so low. Omitting the records of November 7, 17 and 20, the average line comes to 40.8. That there is depression from oil on the 5th, 10th, 13th and 15th is unquestioned. On the other days nervous factors may have been at work with which we could not acquaint

ourselves in the period of nine days which seemed long enough for a control. The great variation in the acidity after the beginning of the administration of oil suggested that it would be of interest to continue the observations, but the patient had to leave before a second series of controls could be carried out. Such controls seem very important in order to allow a proper interpretation of this case. There can be no question but that oil has at various times had a decided depressant effect both on the secretions and the motility.

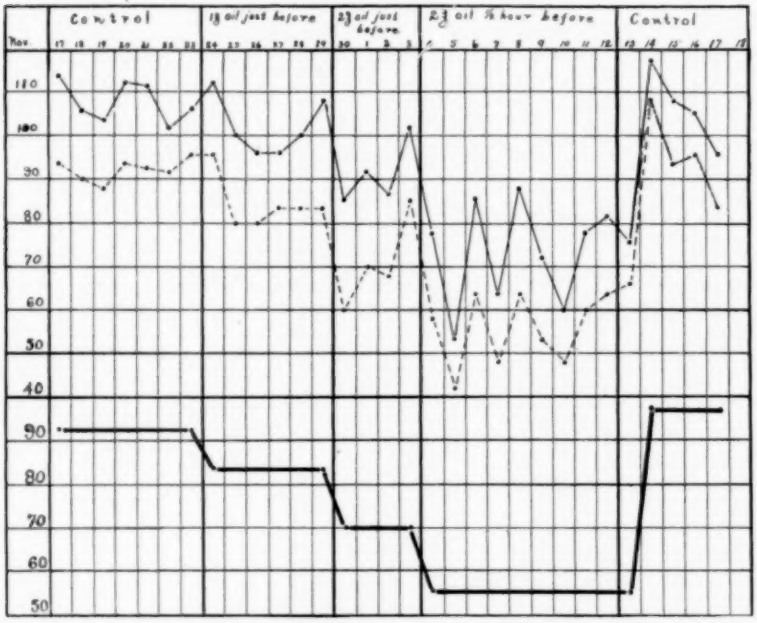

Chart 6, Case 8.—A. P. J. Daily shredded wheat biscuit meals. Upper solid line indicates total acid. Dashed line indicates free acid. Lower and heavy solid line indicates average free acid.

CASE 8.—Mr. A. P. J. Hyperchlorhydria with symptoms. No ulcer.

DAILY MEALS WITH AND WITHOUT OLIVE OIL.

Date.	Amount.	Free HCl.	Total acid.	Peptic value.	Remarks.
November 17, 1903.	40 c.c.	94 c.c.	114 c.c.	1.0	No olive oil.
November 18.....	100	90	106		No olive oil
November 19.....	100	88	104	5.24	No olive oil.
November 20.....	85	94	112	4.4	No olive oil.
November 21.....	82	93	111	4.4	No olive oil.
November 22.....	80	92	102	5.6	No olive oil.

Date.	Amount.	Free HCl.	Total acid.	Peptic value.	Remarks.
November 23.....	60	96	106		No olive oil.
November 24.....	100	96	112		1 oz. immediately before.
November 25.....	100	80	100		1 oz. immediately before.
November 26.....	100	80	96		1 oz. immediately before.
November 27.....	90	84	96		1 oz. immediately before.
November 28.....	110	84	100		1 oz. immediately before.
November 29.....	125	84	108		1 oz. immediately before.
November 30.....	130	60	86		2 oz. immediately before.
December 1.....	95	70	92		2 oz. immediately before.
December 2.....	105	68	87		2 oz. immediately before.
December 3.....	110	86	102		2 oz. immediately before.
December 4.....	110	58	78		2 oz. ½ hr. before.
December 5.....	130	42	54		2 oz. ½ hr. before.
December 6.....	125	64	84		2 oz. ½ hr. before.
December 7.....	80	48	64		2 oz. ½ hr. before.
December 8.....	95	64	88		2 oz. 10 min. before.
December 9.....	100	54	72		2 oz. 10 min. before.
December 10.....	110	48	60		2 oz. 10 min. before.
December 11.....	95	60	78		2 oz. 10 min. before.
December 12.....	105	64	82		2 oz. 10 min. before.
December 13.....	60	66	76		No oil before.
December 14.....	95	108	118		No oil before.
December 15.....	95	94	108	4.00	No oil before.
December 16.....	110	96	106	6.25	No oil before.
December 17.....	90	84	96	5.03	No oil before.

This case was observed for thirty days. The first control series consisted of seven meals. The second control series, beginning on the twenty-sixth day, consisted of five meals, making twelve control meals in all. The effect of dosage, as well as time of administration, of the oil is well illustrated in the average free hydrochloric acid curve. Two ounces of oil immediately preceding the meal causes a decidedly greater depression than one ounce. Two ounces half an hour before the meal brings about a still more marked depression of the secretions. It would seem that in the second instance the increase in the amount of oil accomplished exactly what increase in time before the meal did in the third instance. Two ounces of oil should spread itself over the gastric mucosa more quickly than one ounce. Two ounces half an hour before the meal has still a better chance to cover the entire gastric mucosa, and consequently it may be argued a greater depression should be brought about. That the greater depression in the third instance is not due to prolonged treatment with oil is shown by the rapid rise of the HCl in the second control series to a point even higher than was reached in the first.

C. 22 9.—Mr. L. Hypersecretion with hyperchlorhydria.

EXPERIMENT 1a.

March 9, 1906.—Fasting stomach contained 20 c.c., free HCl 30, total acids 40. After lavage, patient ate a shredded wheat biscuit meal.

Time.	Quantity.	Free HCl.	Total acid.	Pepsin.	Pepsinogen.
7:55	Began eating.				
8:03	Finished eating.				
8:05	13 c.c.	Tr.	7.5 c.c.	0.1	0.6
8:10	13	12.5	15.	5.3	6.7
8:20	14	32.5	37.5	21.1	25.
8:30	12	35	42.5	1.75	
8:40	11.5	32.5	47.5	6.25	10.9
8:50	13	42.5	52.5	18.9	23.
9:00	12	40.	52.5	14.	18.9
9:10	11	35.	50.	16.8	25.
9:20	12	50.	60.	25.	14.
9:30	5	50.	60.	....	....
9:40	4.5	32.5	50.	14.4	
9:43	Lavage shows 5	free HCl.			

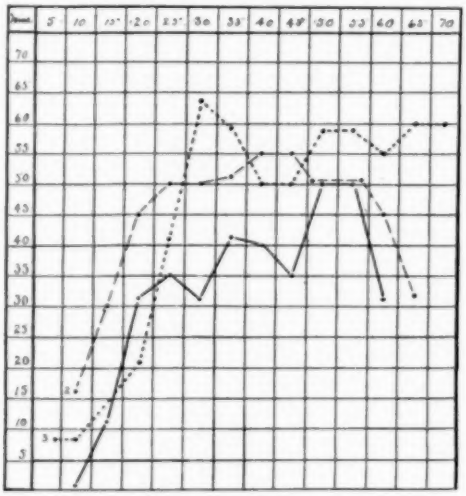

Chart 7, Case 9.—Mr. L. 1, solid line control; 2, line of long dashes, first oil meal, two ounces oil half hour before; 3, line of short dashes, second oil meal, three ounces oil half hour before.

EXPERIMENT 1B.

March 10, 1906.—Fasting stomach, 8 c.c., free HCl 25, total acid 39. After lavage the tube was allowed to remain in the stomach 6 minutes; 5 c.c. was now obtained showing free HCl 20, total acid 30. Peptic value of fasting stomach 41.5, and of the tube stimulation 16.

Time.	Quantity.	Free HCl.	Total acid.	Pepsin.	Pepsinogen.
8:10	Took 2 ounces olive oil.				
8:40	Began eating.				
8:43	Finished eating.				
8:50	7 c.c.	17.5 c.c.	38 c.c.	12.2	18.9
9:00	9.5	30	35	25	
9:10	10.5	45	60		

Time.	Quantity.	Free HCl.	Total acid.	Pepsin.	Pepsinogen.
9:20	11	50	65	25	
9:30	13	50	65	28	
9:40	12	52	70	16.8	18.9
9:50	10	55	70	7.8	
10:00	10	55	71	33.6	18.9
10:10	11	50	68	37.2	26
10:20	10	50	67	....	37
10:30	9	40	58	42.2	23
10:45	5	33	53	....	25
10:47	Lavage.	No free HCl.	5	16	9

EXPERIMENT 1c.

A third meal, given on a date not recorded. Fasting stomach gave 10 c.c., containing free HCl 46, and total acid 60.

Time.	Quantity.	Free HCl.	Total acid.	Pepsin P. V.
6:56	After lavage 3 oz. olive oil was given through a tube.			
7:25	Began eating.			
7:30	Finished eating.			
7:33	9 c.c.	8 c.c.	11	1
7:41	10	8	14	0
7:50	11			
8:00	11	21	38	..
8:10	12.5	42	65	19.3
8:20	12	68	85	19.3
8:30	12	59	70	19.3
8:40	10	50	70	19.3
8:50	10	50	70	16
9:00	12	58	70	22
9:10	10	58	80	23
9:20	10	55	72	25
9:30	13	60	78	32.5
9:40	6	60	77	36

The stomach now appeared empty and as the patient was very tired no lavage was given.

SUMMARY.

	Digestive period.	Amount recovered.
Control meal	1:45	121 c.c.
First oil meal	1:65	118 c.c.
Second oil meal	2:15	148 c.c.

In this case there has been little or no depressant effect on the secretions from the oil. The second oil meal shows changes which simulate those in the preceding meals, a slow rise in the free acid as contrasted with the abrupt rise of the control, increasing gradually, with the exception of the 8:20 sample, 'oward the end of the digestive period, which has been distinctly prolonged. The factor of hypersecretion doubtless plays an important rôle in this case and will be considered later under that head.

SERIES II.

The following cases are those studied at the Craig Colony for Epileptics:

CASE 10.—No. 1416. Mr. H. E. W. Bad heredity. Epilepsy followed typhoid fever. Attacks of grand mal about once a week. No gastric complaints. The test meals consisted of two or two and a half ounces of bread and two glasses of water. Samples were taken every fifteen minutes.

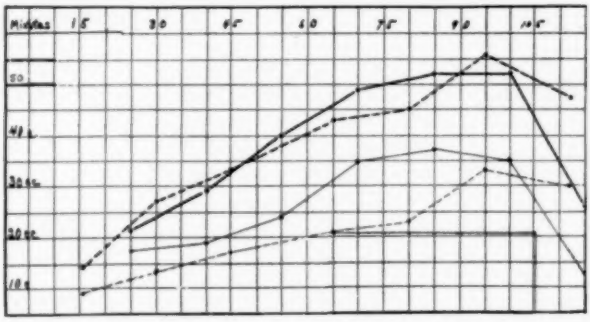

Chart 8, Case 10.—H. E. W. Experiment 1, heavy solid line, total acid of control. Heavy dashed line, total acid of oil meal. Lighter (and lower) dashed line, free acid of oil meal.

EXPERIMENT 1.

June 8, 1906.

Time.	Quantity.	Free HCl.	Total acid.
8:25	Began eating.		
8:48	Finished eating.		
8:50	20 c.c.	17.5 c.c.	21.5 c.c.
9:05	20	18.5	29
9:20	26	24	40
9:35	25	35	49
9:50	21	37.5	52
10:05	30	35	52.5
10:20	8	13.3	26.6

Free HCl, highest, 37.5, at 85 min. Amount recovered, 150 c.c.

June 9, 1906.—Same test breakfast as above.

Time.	Quantity.	Free HCl.	Total acid.
7:45	0.75 oz. cotton seed oil.		
8:20	Began eating.		
8:31	Finished eating.		
8:36	10 c.c.	9 c.c.	14 c.c.
8:50	25	13.5	22.7
9:05	30	17	33
9:25	25	21.5	43.5
9:40	25	23	45
9:55	24	33.4	56.2
10:12	5	30	47.5

Free HCl, highest, 33.4, at 95 min. Amount recovered, 144 c.c.

EXPERIMENT 2.

June 11, 1906.—Shredded wheat biscuit meal.

Time.	Quantity.	Free HCl.	Total acid.
8:24	Began eating.		
8:34	Finished eating.		
8:36	28 c.c.	3.7 c.c.	8.7 c.c.

Time.	Quantity.	Free HCl.	Total acid.
8:52	27	18.5	26
9:12	28	30	41
9:26	25	32	43
9:43	20	42.5	55
10:01	20	41	54
10:20	12	38	48
10:40	4	30	35

Highest free HCl, 42.5, at 79 min.; 164 c.c. recovered.

June 12, 1906.

Time.	Quantity.	Free HCl.	Total acid.
7:30	2 oz. oil per tube.		
8:02	Began eating.		
8:10	Finished eating.		
8:12	22 c.c.	6 c.c.	10.4 c.c.
8:28	20	8	17
8:43	30	24	33.5
9:03	30	34	46
9:20	20	46	58
9:36	20	43	57
9:53	10	..	..

Highest free HCl, 46, at 78 min. Recovered 152 c.c.

This patient had an epileptic attack about 7:30 a. m. preceding the control meal. He came to the laboratory at 8:15, complaining of a headache, and was slightly confused.

EXPERIMENT 3.

June 14, 1906.—Shredded wheat biscuit meal.

Time.	Quantity.	Free HCl.	Total acid.
8:25	Began eating.		
8:34	Finished eating.		
8:35	50 c.c.	7.5 c.c.	11 c.c.
8:50	20	22	33
9:05	20	40	52
9:20	20	35	48
9:35	20	50.7	61
9:50	10	57	67

Free HCl, highest, 57, at 85 min. Amount recovered, 140 c.c.

June 15, 1906.—Shredded wheat biscuit meal with oil.

Time.	Quantity.	Free HCl.	Total acid.
7:00	Oil, 2 oz.		
7:32	Began eating.		
7:38	Finished eating.		
7:40	15 c.c.	6 c.c.	11 c.c.
7:55	15	16	21
8:10	15	18	26
8:25	15	28	38
8:40	15	48.3	57.3
8:55	15	57	69
9:10	15	56.6	68.3
9:25	10	50	60

Free HCl, highest, 57, at 83 min. Amount recovered, 115 c.c.

EXPERIMENT 4.—DAILY MEALS.

Date.	Last seizure.	Quantity.	Free HCl.	Total acid.	
June 19	G. 9:40 p. m.				
June 20	.....	150 c.c.	73 c.c.	86 c.c.	...
July 5	G. 5 p. m.	90	66	80	...
July 6	.....	40	66	76	...
July 7	.....	110	54	68	...
July 9	.....	110	46	56	...
July 10	.....	110	55	69.6	...
July 26	.....	105	54	66	Oil.
July 27	.....	38	50	62	Oil.
July 28	.....	110	63	72	Oil.
July 29	G. 12:25 p. m.				
July 30	.....	12	60	88	Oil.
August 1	.....	70	77	89	Oil.
August 2	.....	90	56	65	...

Total number of daily meals, 12.
Average of 7 meals without oil, HCl, 59.4; total acid, 71. Amount, 100 c.c.
Average of 5 meals with oil, HCl, 60.8; total acid, 75. Amount, 67 c.c.

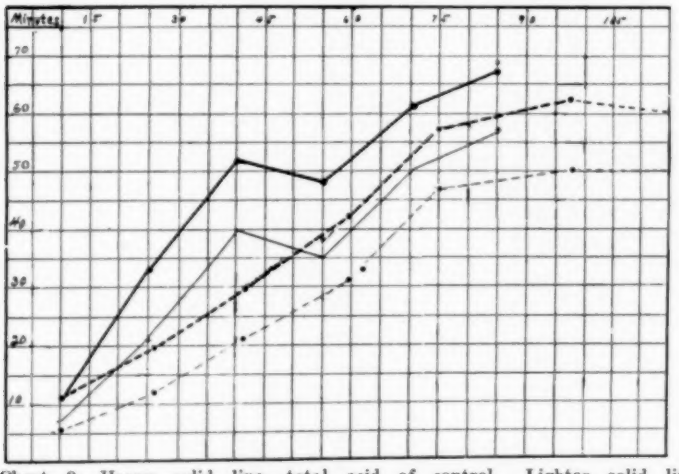

Chart 9.—Heavy solid line, total acid of control. Lighter solid line, HCl of control. Heavy dashed line, total acid for oil meal, being an average of experiments 2 and 3. Lighter (and lower) dashed line, HCl after oil meal, average of experiments 2 and 3.

SUMMARY.

In this case four experiments were conducted, three special meals and one series of daily meals. The results may be summed up as follows: There is distinct evidence of a depressant effect from oil in all of the special meals. With the control meals the rise of the HCl curve is quicker in all cases, except in Experiment 3. The rate of the secretion

is decidedly lowered by oil, being twenty minutes behind the control in Experiment 1 and about twenty minutes behind the control in Experiment 2. The height of digestion is reached at the end of the digestive period instead of the middle, as in the case of the control in Experiments 1 and 2, while in Experiment 3 practically no change can be noted.

Experiment 4 shows no depressant effect from the oil, but rather a reverse of what has been noted heretofore. In none of the experiments has there been any lowering of the motor power, and in Experiment 4 there seems to be a distinct increase in the motor power.

CASE 12.—Mr. W. Grand mal. No gastric symptoms. Test meals of dry toast and water.

EXPERIMENT 1.

Time.	Quantity.	Free HCl.	Total acid.
7:40	Began eating.		
7:45	Finished eating.		
7:55	22 c.c.	2 c.c.	8 c.c.
8:15	20	11.2	23.2
8:40	20	16	32
9:00	30	16	28
9:20	6	15	32.5

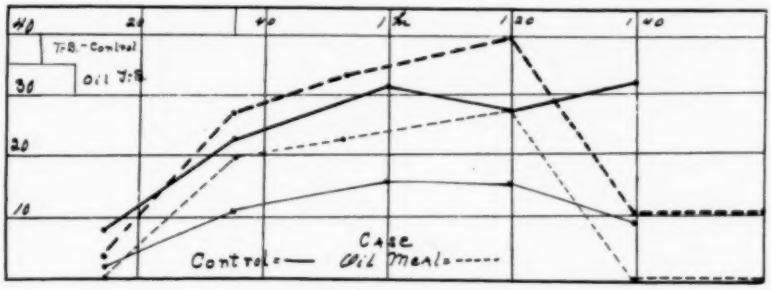

Chart 10, Case 12.

June 28, 1906.—Attack at 12:50 p. m.

Time.	Quantity.	Free HCl.	Total acid.
7:05	Oil given.		
7:40	Began eating.		
7:50	Finished eating.		
7:55	20 c.c.	0 c.c.	4 c.c.
8:15	20	20	27
8:33	20	23	34
9:00	20	27.5	40
9:20	20	Trace	12
9:40	15	0.0	12.5

EXPERIMENT 2.—DAILY MEALS.

Date.	Quantity.	Free HCl.	Total acid.	
June 23	90 c.c.	32 c.c.	44 c.c.	
June 26	55	38	48	
June 29	4	2	3	
July 3	200	8	16	Oil.
July 5	90	18	30	
July 6	?	26	36	
July 7	65	13	25	
July 9		10	20	Oil.
July 10	95	37	50	Oil.
July 26	18	00	..	Oil.
July 27	76	14	26	Oil.
July 28	80	16	27	

Average of 7 control meals: HCl, 20.7; total acid, 28; amount, 64.
Average of 5 oil meals: HCl, 14; total acid, 28; amount, 92.

SUMMARY.

Experiment 1.—The acidities with the oil were all distinctly higher than with the control. There is, however, a slowing of the rate of secretion in the oil meal, as well as a lowering of the motility. As the observations were made only at intervals of twenty minutes, the extent of the lowering of the rate of secretion can not be determined. The oil meal preceded an epileptic seizure by only a few hours. This may account for the increase in the acidities and the disappearance of the free HCl in the last samples.

Experiment 2.—Twelve meals were given in this series. There is distinct depression of the acidity from the oil and a lowering of the motility. If the averages are compared, distinct depression and decreased motility are noted. In the control meals, taken at random, there is a variation in the free acid values of from 2 to 32, while a corresponding change takes place in the total acid values. It is, therefore, impossible to maintain that the apparent depression in the oil meals is due to oil.

Attacks of the grand mal occurred June 24, at 12:15 p. m., and July 27, at 9:35 p. m. It may be noteworthy that the attack on June 24 was followed by almost complete absence of free acid, and that the attack of July 27 was preceded by a similar observation.

A case showing such wide variations is not suitable for experimentation. The record is presented here because the results of the special meal followed the general rule, showing a decrease in the rate of secretion with oil, and also because it may serve as an illustration of the possible outcome of observations taken at intervals so widely separated—ten days in one instance.

CASE 13.—Mr. A. H. Grand mal. No gastric complaints.

EXPERIMENT 1.

Probably June 17, 1906.

Time.	Quantity.	Free HCl.	Total acid.
8:52	Began eating.		
8:59	Finished eating.		
9:00	15 c.c.	0 c.c.	2 c.c.
9:20	15	8	12
9:35	15	13.5	20
9:50	20	12	34
10:05	17	27	38
10:17	20	18	29
10:36	20	20	32
10:57	35	38	54
11:12	15	22	35
11:27	15	12	24

EXPERIMENT 2.

June 18, 1906.

Time.	Quantity.	Free HCl.	Total acid.
7:00	Oil given.		
7:30	Began eating.		
7:36	Finished eating.		
7:40	15 c.c.	0 c.c.	4 c.c.
7:55	15	16	24
8:10	18	9	13
8:25	20	42	56
8:40	15	40	51
8:55	15	20	34.6
9:10	..	31	42.5
9:25	20	22	35
9:40	15	36.3	49.5
10:00	15	25	40

EXPERIMENT 3.

June 27, 1906.—Dry toast meal. Epileptic seizure the night before experiment.

Time.	Quantity.	Free HCl.	Total acid.
7:45	Began eating.		
7:52	Finished eating.		
8:00	20 c.c.	1 c.c.	4 c.c.
8:20	25	32	41
8:45	10	39	48

Stomach empty.

SUMMARY OF DAILY MEALS.

Date.	Quantity.	Free HCl.	Total acid.	Oil.	Seizures.
June 19	100 c.c.	60 c.c.	74 c.c.		
June 20	120	58	73		
June 21	45	46	60		
June 22	70	70	82		
June 23	55	64	74		
June 24	..	..	..		G. M., 11:35 p. m.
June 26	10	18	24		
June 28	20	12.5	75	Oil.	
June 29	10	26	42	Oil.	

Date.	Quantity.	Free HCl.	Total acid.	Oil.	Seizures.
July 3.....	110	9.9	22	Oil.	Attack before meal.
July ?.....	75	62	76		9th, 5:20 a. m.
July 10.....	90	27	42		
July 6.....	10	50	90		
July 7.....	80	61	75		
July 9.....	25	56	66		
July 26.....	120	55	63		5:00 a. m.
July 28.....	78	26	42	Oil.	
Averages.—					
12 meals.....	66.6	55.5	70.6	No oil.	
4 meals.....	54	18.6	45	With oil.	

An inspection of the tables in this case shows that with the special meals the acidity was somewhat higher after the oil than after the control meals. The quantity recovered with oil is smaller than without.

The tests following daily meals show that with oil the quantity is somewhat decreased, while the acids are markedly lower than in control meals.

CASE 14.—Mr. H. Grand mal.

EXPERIMENT 1.—SPECIAL MEALS.

June 22, 1906.—Samples taken every 15 min. No seizures.

Time.	Quantity.	Free HCl.	Total acid.
7:30	Began eating.		
7:36	Finished eating.		
7:40	20 c.c.	4 c.c.	8 c.c.
7:55	22	25	30
8:05	15	36	44
8:15	15	38	50
8:46	10	..	..

June 23, 1906.—Samples fifteen minutes apart.

Time.	Quantity.	Free HCl.	Total acid.
7:39	Oil given.		
8:00	Began eating.		
8:05	Finished eating.		
8:06	15 c.c.	10 c.c.	22.5 c.c.
8:20	20	16	27
9:15	Stomach empty.		

June 28, 1906.—Samples every twenty minutes. No seizures.

Time.	Quantity.	Free HCl.	Total acid.
7:05	Oil given.		
7:40	Began eating.		
7:50	Finished eating.		
7:55	20 c.c.	4 c.c.	8 c.c.
8:15	22	7	15
8:32	22	9	20
8:55	15	9	20
9:15	19	13.3	30

EXPERIMENT 2.—DAILY HOURLY MEALS.

Date.	Quantity.	Free HCl.	Total acid.	Seizures.	
June 26.....	19 c.c.	55 c.c.	66 c.c.	None.	No oil before.
June 27.....	8	..	..	None.	Oil before.
July 3.....	160	24	36	None.	No oil before.
July 5.....	100	48	64	None.	No oil before.
July 6.....	5	20	30	None.	No oil before.
July 7.....	75	69	85	None.	No oil before.
July 9.....	75	60	72	G.M., 6:40 a.m.	No oil before.
July 19.....	200	48	62	None.	Oil before.
July 27.....	..	16	27	None.	Oil before.
July 28.....	10	..	..	None.	Oil before.
July 30.....	280	Tr.	12	None.	Oil before.
July 31.....	20	20	32	None.	No oil before.
August 1.....	155	22	32	None.	Oil before.
Averages.....	47.5	45.3	58	Without oil.	
	116	22.5	34	With oil before the meal.	

This patient had epileptic seizures as follows: June 22, grand mal at 5:50 a. m.; June 29, grand mal, 10:40 p. m.; July 9, grand mal at 6:40 a. m.; July 29, grand mal at 12:50 a. m. It is of interest to note that on the day following the last seizure free HCl was present only in traces.

SUMMARY.—Experiment 1.—No depression is seen from oil in the first oil meal. The stomach emptied itself very quickly. The second oil meal shows a delay in the appearance of acid, a decrease in the amount at the height of digestion, and a prolongation of the digestive period, the height of which was reached at its end.

It will be observed that the average acidity of the oil meals was lower while the quantity recovered was increased.

CASE 15.—Mr. R. C. P. Epilepsy of unknown cause. Attacks of grand mal and petit mal. At one time there was an aura consisting of a sensation of cold in the stomach and a quickening of the heart. No gastric symptoms.

EXPERIMENT 1.

June 18, 1906.—Shredded wheat biscuit meal.

Time.	Quantity.	Free HCl.	Total acid.
7:54	Began eating.		
7:59	Finished eating.		
8:00	15 c.c.	0 c.c.	8 c.c.
8:16	15	4.6	12
8:30	15	14	20
8:45	15	0	10
9:00	15	16	25
9:15	15	10	16

June 19, 1906.—Shredded wheat biscuit and oil.

Time.	Quantity.	Free HCl.	Total acid.
7:00	Oil taken.		
7:32	Began eating.		
7:38	Finished eating.		
7:40	15 c.c.	0 c.c.	2 c.c.
7:55	15	0	6
8:10	15	0	0
8:25	15	2	6
8:40	15	10	20

EXPERIMENT 2.

Daily meals of shredded wheat biscuit until June 25, inclusive; toast meals thereafter.

Date.	Quantity.	Free HCl.	Total acid.	Oil.	Seizures.
June 20	90 c.c.	46.8 c.c.	58 c.c.	Control.	P.M., 1:20 p.m.
June 21	55	50	62	Control.	Mild, 2:40 a.m.
June 22	45	51	64	Control.	
June 23	12	51	64	Control.	
June 25	20	12	19	Control.	G., 10 p. m.
June 26	5	25	35	Control.	
July 3	190	8	16	Oil.	
July 5	40	30	40	Oil.	
July 6	80	56	66	Control.	
July 7	45	57	71	Control.	
July 9	35	25	44	Oil.	
July 10	..	17	35	Oil.	
July 26	148	11	20	Oil.	
July 27	58	31	41	Oil.	
July 28	2	10	20	Oil.	

Averages of 9 control meals: HCl, 39.8; total acid, 51; amount, 39.
Averages of 6 oil meals: HCl, 20.3; total acid, 32; amount, 94.

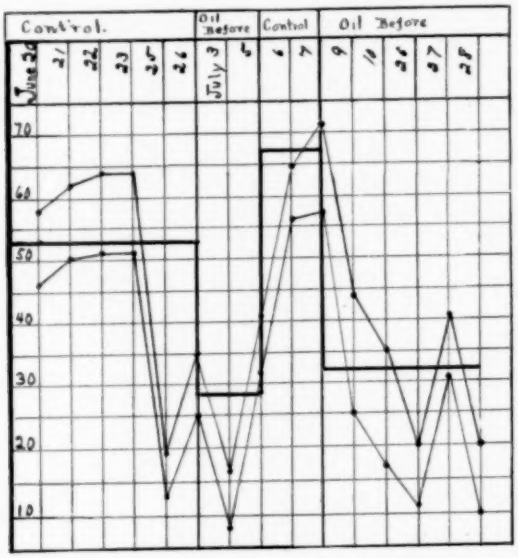

Chart 11, Case 15.—Experiment 2, heavy line, average total acid.

SUMMARY.

Experiment 1 shows what thus far seems to be the rule with the special meals, namely, a depression of the acidity by oil, a decrease in the rate of secretion, which continues at its height to the end of the digestive

period or reaches its highest point only at that time. The motility was unaffected by the oil.

Experiment 2.—Fifteen meals were given in this series, 9 without oil and 6 with oil. The secretion was distinctly depressed by the oil and the evacuation of the stomach lengthened.

CASE 16.—Mr. G. S. Grand mal.

SUMMARY OF DAILY MEALS.

Date.	Quantity.	Free HCl.	Total acid.	Oil.	Seizures.
July 5.....	4 c.c.	20 c.c.	40 c.c.	Control.	
July 6.....	10	40	50	Control.	
July 7.....	5	17.5	30	Control.	
July 9.....	5	15	32.5	Control.	
July 10.....	10	22.5	32.5	Control.	
July 26.....	45	43.4	53.4	Control.	
July 27.....	8	0	..	Oil.	
July 28.....	10	5	10	Oil.	
July 30.....	8	10	20	Oil.	G. 1, a. m.
July 31.....	2	0	5	Control.	
August 1.....	9	14	20	Control.	
August 2.....	8	20	40	Oil.	G. 2, night.
August 3.....	8	Tr.	5	Oil.	
Averages.—					
Control.....	11.2	21.5	33		
Oil meals.....	8.4	7.0	19		

In this case attention should be called to the fact that up to the time of giving oil on the 27th, the lowest free HCl acidity was 15. The apparent effect of the oil was to reduce the secretion from 43.4 on the 26th to 0 on the 27th. On the 30th, following the administration of oil, the free acid was 10, while on the succeeding day without oil, its value was 0. On the next day free HCl reappeared and on August 2, notwithstanding the administration of oil, the record was a little higher.

Clinical and experimental experience tends to teach us that the effect of a dose of oil does not persist throughout the following day or even through the next meal. Its action seems to be limited to the period immediately following its administration.

When one considers these records the following questions arise:

(1) Was the low acidity found between July 27 and 30 dependent on nervous factors, and was its association with the administration of oil merely a coincidence?

(2) Was this low acidity, on the other hand, due to a true depressant action of the oil and were the low values of July 31 and August 1 the result of a persistence of one's depressing influence?

CASE 17.—Mr. L. R.

SUMMARY OF DAILY MEALS.

Date.	Quantity.	Free HCl.	Total acid.	Oil.	Seizures.
July 5.....	15 c.c.	34 c.c.	46 c.c.	Control.	July 5, 1 p. m.
July 7.....	35	33	51	Control.	
July ?	40	37	54	Control.	
July 10.....	30	41	57	Control.	
July 26.....	8	53	63	Control.	July 25, 1 a. m.
July 27.....	28	15	25	Oil.	
July 28.....	155	4	12	Oil.	
July 30.....	170	10	18	Oil.	
July 31.....	12	23	33	Control.	
August 1.....	130	18	25	Oil.	
August 2.....	30	11	26	Oil.	Aug. 3, 1 a. m.
Averages.—					
No oil.....	23	37	50	All attacks petit mal.	
With oil.....	102	12	21	All attacks petit mal.	

CASE 18.—Mr. C. M.

SUMMARY OF DAILY MEALS.

Date.	Quantity.	Free HCl.	Total acid.	Oil.	Seizures.
July 5.....	22 c.c.	40 c.c.	50 c.c.	Control.	
July 6.....	10	30	40	Control.	
July 7.....	120	48	65	Control.	
July 9.....	20	47	61	Control.	
July 10.....	145	37	51	Control.	
July 26.....	120	38	48	Control.	
July 27.....	50	30	50	Oil.	
July 28.....	240	0	6	Oil.	July 29, a. m.
July 30.....	..	29	41	Oil.	
July 31.....	75	40	54	Control.	July 31, a. m.
August 1.....	45	6	20	Oil.	
August 2.....	20	20	34	Oil.	
Averages.—					
No oil.....	40	51	71		Petit mal.
With oil.....	17	30	90		Petit mal.

In this series the control meals show free HCl values between 30 and 48, while the oil meals show a drop to below 30. The increase in the free HCl value on July 31 is of interest because oil did not precede the meal.

CASE 19.—Mr. F. K.

SUMMARY OF DAILY MEALS.

Date.	Quantity.	Free HCl.	Total acid.	Oil.	Seizures.
July 5.....	10 c.c.	6 c.c.	8 c.c.	Control.	G., a. m.
July 6.....	5	30	40	Control.	P., a. m.
July 7.....	15	44	58	Control.	
July 9.....	100	40	52	Control.	
July 10.....	8	5	12	Control.	P., a. m.
July 25.....	..	..	..		P., 25, a. m.
July 26.....	120	51	66	Control.	2 P., 26, a. m.
July 27.....	35	32	46	Oil.	P., 27, a. m.

Date.	Quantity.	Free HCl.	Total acid.	Oil.	Seizures.
July 28.....	40	0	10	Oil.	G., 28, a. m.
July 30.....	340	14	23	Oil.	
July 31.....	15	15	33	Control.	
August 1.....	80	58	70	Control.	
August 2.....	55	26	39	Oil.	P., a. m.
Averages.—					
No oil.....	44	31.0	85		2 G. mal.
With oil.....	107	18	29		6 P. mal.

CASE 20.—Mr. G. S.

Date.	Quantity.	Free HCl.	Total acid.	Oil.	Seizures.
July 5.....	15 c.c.	24 c.c.	42 c.c.	Control.	
July 6.....	42	50	70	Control.	P., a. m.
July 7.....	10	11	23	Control.	P., July 7, a. m.
July —.....	30	26	45	Control.	P., July 8, a. m.
July 10.....	15	11.6	25	Control.	P., a. m.
July 25.....	..	..	..		P., July 25, a. m.
July 26.....	30	27	39	Control.	P., July 26, a. m.
July 27.....	50	10	23	Oil.	
July 28.....	50	0	4	Oil.	
July 30.....	50	31	41	Oil.	
July 31.....	90	32	45	Control.	
August 1.....	25	31	46	Control.	
August 2.....	110	7	16	Oil.	
Averages.—					
No oil.....	32	26.5	42		
With oil.....	65	12	21		

CASE 21.—Mr. B. C.

SUMMARY OF DAILY MEALS.

Date.	Quantity.	Free HCl.	Total acid.	Oil.	Seizures.
July 6.....	55 c.c.	30 c.c.	40 c.c.	Control.	G. M.
July 7.....	120	19	38	Control.	
July 9.....	35	12	26	Control.	P. M.
July 10.....	75	21	39	Control.	
July 26.....	75	20	36	Control.	
July 27.....	100	6	20	Oil.	
July 28.....	60	14	26	Oil.	
July 30.....	200	6	18	Oil.	
July 31.....	115	22	34	Control.	
August 1.....	110	21	32	Oil.	
August 2.....	50	23	33	Oil.	
Averages.—					
No oil.....	79	21	35		
With oil.....	104	14	26		

CASE 22.—Mr. A. L. No seizures during experiment.

SUMMARY OF DAILY MEALS.

Date.	Quantity.	Free HCl.	Total acid.	Oil.
August 6.....	90 c.c.	33 c.c.	49 c.c.	Control.
August 8.....	50	37	52	Control.
August 9.....	45	29	44	Control.
August 10.....	45	28	46	Oil.
August 11.....	..	40	58	Oil.
August 13.....	36	20	35	Oil.
August 14.....	100	27	34	Oil.
Averages.—				
No oil.....	61	30	48	
With oil.....	60	29	46	

CASE 23.—Mr. H. Y. No seizures during experiment.

SUMMARY OF DAILY MEALS.

August 4	80 c.c.	23 c.c.	33 c.c.	Control.
August 6	30	36	47	Control.
August 7	30	34	45	Control.
August 8	25	32	43	Control.
August 9	72	9	16	Oil.
August 10	50	30	50	Oil.
August 11	170	10	23	Oil.
August 13	55	37	48	Oil.
Averages.—				
With oil	87	21	34	
No oil	41	31	42	

CASE 24.—Mr. R. W.

SUMMARY OF DAILY MEALS.

Date.	Quantity.	Free HCl.	Total acid.	Oil.	Seizures.
August 4	8 c.c.	15 c.c.	25 c.c.	Control.	G. M., a. m.
August 6	23	36.4	48	Control.	G. M., a. m.
August 7	60	60	78	Control.	G. M., a. m.
August 8	12	30	50	Control.	
August 9	12	6	20	Oil.	
August 10	15	20	36	Oil.	
August 11	20	20	37.5	Oil.	
August 12	..	..	..		G.M.,Aug.12, a.m.
August 13	10	17.5	32.5	Oil.	
August 14	..	..	..		G.M.,Aug.14, a.m.
Averages.—					
No oil	26	35.3	50		
With oil	14	16	31.5		

CASE 25.—Mr. W. C.

Date.	Quantity.	Free HCl.	Total acid.	Oil.	Seizures.
August 4	50 c.c.	19 c.c.	42 c.c.	Control.	
August 6	55	31	50	Control.	
August 7	22	20	34	Control	2 G. M., a. m.*
August 8	50	18	32	Control.	
August 9	35	11	23	Control.	
August 10	45	8	24	Oil.	2 p. m.
August 11	35	33	47	Oil.	
August 13	115	15	32	Oil.	
August 14	70	40	54	Oil.	
August 15	..	..	..		Aug. 15, 2 p. m.
Averages.—					
With oil	66	24	39		
No oil	42	20	36		

NOTE.—This case shows little change in the acidity, while after the administration of oil the evacuation is delayed.

CASE 26.—J. E. No. 1992. No seizures during experiment.

SUMMARY OF DAILY MEALS.

Date.	Quantity.	Free HCl.	Total acid.	Oil.
August 4	115 c.c.	34 c.c.	48 c.c.	Control.
August 6	30	16	35	Control.
August 7	95	34	55	Control.
August 8	4	15	30	Control.
August 9	12	14	32	Control.
August 10	12	22	38	Control.

Date.	Quantity.	Free HCl.	Total acid.	Oil.
August 11	12	10	27.5	Control.
August 12	15	?	20	Control.
August 14	105	23	41	Oil.
August 15	74	16	36	Oil.
August 16	170	30	48	Oil.
August 17	45	28	44	Oil.
August 18	22	19	37	Oil.
Averages.—				
No oil	37	19	35.6	
With oil	83	23	41	

CASE 27.—R. B. No. 1045. No seizures during experiment.

SUMMARY OF DAILY MEALS.

Date.	Quantity.	Free HCl.	Total acid.	Oil.
August 4	15 c.c.	8 c.c.	17 c.c.	Control.
August 6	15	30	50	Control.
August 7	10	16	27	Control.
August 8	5	20	37.5	Control.
August 9	8	30	50	Control.
August 10	40	32	52	Oil.
August 11	50	18	43	Oil.
August 13	42	15	30	Oil.
August 14	94	20	38	Oil.
Averages.—				
No oil	11	21	36	
With oil	56	21	41	

The oil had apparently no effect in this case except to decrease the motility.

CASE 28.—H. S. No. 885. No seizures during experiment.

SUMMARY OF DAILY MEALS.

Date.	Quantity.	Free HCl.	Total acid.	Oil.
August 5	12 c.c.	40 c.c.	51 c.c.	Control.
August 6	0	..	..	Control.
August 7	20	38	50	Control.
August 8	10	31	41	Control.
August 9	10	10	16.6	Oil.
August 11	125	10	35	Oil.
August 13	15	0	5	Oil.
Averages.—				
No oil	14	36.3	47	
With oil	50	6	18.7	

CASE 29.—W. H. No. 1278. No seizures during experiment.

SUMMARY OF DAILY MEALS.

Date.	Quantity.	Free HCl.	Total acid.	Oil.
August 4	40 c.c.	20 c.c.	32 c.c.	Control.
August 6	80	24	40	Control.
August 7	45	31	47	Control.
August 8	35	30	43	Control.
August 9	55	17	31	Oil.
August 10	290	9	22	Oil.
August 11	70	18	32	Oil.
August 13	25	41	50	Oil.
Averages.—				
With oil	110	21	36	
No oil	50	29	40.5	

CASE 30.—W. M. No. 1096. No seizures.

SUMMARY OF DAILY MEALS.

Date.	Quantity.	Free HCl.	Total acid.	Oil.
August 6	20 c.c.	32 c.c.	54 c.c.	Control.
August 7	12	14	22	Control.
August 8	12	35	53	Control.
August 9	12	42	57	Control.
August 10	115	20	40	Oil.
August 11	165	20	33	Oil.
August 13	14	20	35	Oil.
Averages.—				
No oil	14	29.5	46.5	
With oil	98	20	35	

CASE 31.—F. K. No. 1889. No seizures.

SUMMARY OF DAILY MEALS.

Date.	Quantity.	Free HCl.	Total acid.	Oil.
August 4	28 c.c.	14 c.c.	29 c.c.	Control.
August 6	18	23	42	Control.
August 7	95	32	50	Control.
August 8	8	18	26	Control.
August 9	10	25	40	Control.
August 10	240	8	22	Oil.
August 11	290	13	27	Oil.
August 13	170	29	42	Oil.
August 14	35	16	20	Oil.
August 15	98	49	62	Oil.
August 16	135	42	54	Oil.
Averages.—				
With oil	161	26	38	
No oil	32	22.4	37	

CASE 32.—J. W.

SUMMARY OF DAILY MEALS.

Date.	Quantity.	Free HCl.	Total acid.	Oil.
August 6	5 c.c.	15 c.c.	30 c.c.	Control.
August 7	8	32	40	Control.
August 9	18	17.5	35	Control.
August 10	72	40	56	Control.
August 11	12	20	35	Control.
August 13	12	0	15	Control.
August 14	18	6	18	Oil.
August 15	42	17	28	Oil.
August 16	50	12	23	Oil.
August 17	82	9	23	Oil.
August 18	40	0	..	Oil.
Averages.—				
No oil	21	24.9	29.2	
With oil	48.4	10	33	

CASE 33.—Mr. A. K. (This case was overlooked and is not included in the summaries.)

EXPERIMENT 1.

June 20, 1906.

Time.	Quantity.	Free HCl.	Total acid.
7:45	Began eating.		
7:50	Finished eating.		
7:52	15 c.c.	2 c.c.	6 c.c.
8:05	15	16	26
8:24	20	25	36
8:48	16	43	58

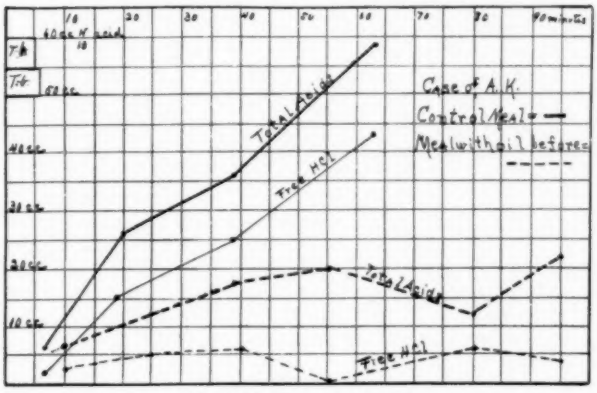

Chart 12, Case 33.—A. K.

EXPERIMENT 2.

June 21, 1906.

Time.	Quantity.	Free HCl.	Total acid.
7:00	Oil taken.		
7:30	Began eating.		
7:36	Finished eating.		
7:40	15 c.c.	2 c.c.	6 c.c.
7:55	20	5	12
8:10	15	5.4	17.4
8:25	15	0	20
8:50	15	6	12
9:05	20	4	22

A marked lowering of the acidity will be observed in the meal preceded by oil. On the next day, in 70 minutes, the free acid was 71 and the total acidity 87; on the 23d, 42 and 51. The diminution was therefore exactly coincident with the administration of oil.

The cases reported in the epileptic series were observed wholly by Dr. Munson. In connection with these cases, there were factors, the consideration of which will be taken up by him in a separate paper. The patients were all taking the bromid treatment, and, as this was a constant factor, we may assume that the effect, whatever it may have been, was constant. From a consideration of this series it would seem that an epileptic seizure does not exercise any definite influence on the gastric

secretion. At times a lowering of the acid values is observed before the seizure, while again a similar condition may follow the attack. When the cases of this series are taken collectively and considered critically, they are seen, for the greater part, to follow closely the rules established by the University Hospital cases.

The following table, comprising 310 stomach analyses of the daily meal series, has been compiled for the purpose of showing the average quantity and acidities of control meals, without oil, compared with meals preceded half an hour by oil:

TABLE 1.

Case.	Number of Meals.		Quantity.		Free HCl.		Total acid.	
No.	Control.	Oil.	Control.	Oil.	Control.	Oil.	Control.	Oil.
5	15	9	40	158	51	21	65	34
6	8	5	74	199	62.5	25.7	73	41
7	9	16	64	106	49	40.5	66.2	55
8	12	9	84	105	91	55.5	104.9	62.2
10	7	5	100	67	59	60.8	71	75
12	7	5	64	92	20.7	14	28	28
13	12	4	66	54	55.5	18.6	70.6	45
14	7	6	47.5	116	45.3	22.5	58	34
15	8	7	44	67.5	43.6	18.8	53.8	30.8
16	8	5	11.2	8.4	21.5	7	33	19
17	6	5	23	102	37	12	50	21
18	7	5	71	90	40	17	51	30
19	8	4	44	107	31	18	85	29
20	8	4	32	65	26	12	42	21
21	6	5	79	104	21	14	35	26
22	3	4	61	60	30	29	48	46
23	4	4	41	87	31	21	42	34
24	4	4	26	14	35.3	16	50	31
25	5	4	42	66	20	24	36	39
26	8	5	37	83	19	23	35.6	41
27	5	4	56	11	21	21	41	36
28	4	3	14	50	36	6	47	18.7
29	4	4	50	110	29	21	40.5	36
30	4	3	14	98	29.5	20	46.5	35
31	5	6	32	161	22.4	26	37	38
32	6	5	21	46.4	20.6	8.8	35	18.4
Averages of all meals			43.3	85.6	36.4	22.4	51.3	35.5

From the compilation of the averages of these 26 cases the following observations may be made:

(a) The motility was decreased in 18 cases,[9] increased in 5 cases,[8] unchanged in 3 cases.[10]

8. Cases 10, 18, 16, 24, 27.

9. Cases 5, 6, 12, 14, 15, 17, 18, 19, 20, 21, 23, 25, 26, 28, 30, 31, 32.

10. Case 22.

(b) The free acid was decreased in 19 cases,[11] increased in 0 cases, unchanged in 6 cases.[12]

(c) The total acidity was increased in 17 cases,[13] increased in 0 cases, unchanged in 8 cases.[14]

A true estimate of the action of oil on the gastric functions may be obtained by comparing the following averages of the 170 control meals with the 140 meals preceded by oil, for in these individual characteristics and modifying circumstances will be eliminated almost completely.

	Quantity.	Free HCl.	Total Acidity.
Controls	43.3	36.4	51.3
Oil meals	85.6	22.04	35.5

For this series of 310 meals, withdrawn one hour from the beginning of ingestion, it may be concluded that the administration of two ounces of oil, half an hour before the meal, delays the evacuation of the stomach and decreases the acidity markedly.

TABLE 2.

Case No.	No. of meal.	Beginning of secretion in the oil meals.	Free acid value of oil meal after 1 hr., compared with control.	Height of secretion reached in the		Ultimate height of secretion with the oil meals compared with controls.	End of secretion reached with	
				Control in min.	Oil meal in min.		Control in min.	Oil meal in min.
5	1	Delayed 10 min.	Decreased.	65	70	Lower.	85	90
	2	Unchanged.	Decreased.	65	85	Lower.	85	95
6	3	Delayed 10 min.	Decreased.	45	140	Higher.	75	140
9	4	Unchanged.	Same.	50	40	Same.	60	65
	5	Hastened.	Increased.	50	30	Higher.	60	70
10	6	Hastened.	Decreased.	85	95	Higher.	115	115
	7	Unchanged.	Increased.	79	78	Higher.	136	111
	8	Unchanged.				Higher.	110	113
12	9	Unchanged.	Increased.	85	83	Lower.	100	120
13	10	Unchanged.	Increased.	80	80	Higher.	155	150
14	11	Increased.	Increased.	125	55	Lower.	76	75
	12	Delayed 5 min.	Decreased.	45	20	Lower.	76	95
15	13	Delayed 31 min.	Decreased.	45	95	Same.	83	68
33	14	Delayed 5 min.	Decreased.	66	68	Lower.	63	95
			Decreased.	63	80			
Averages..		5 delayed.	8 decr.	4 hastened.		6 lower.	8 prolonged.	
		3 hastened.	5 incr.	7 prolonged.		6 higher.	2 shortened.	
		6 unchanged.	1 same.	3 unchanged.		2 same.	4 unch'ng'd.	

In the special meal series a few additional points are demonstrated. An interpretation of the action of oil in producing the above effects is

11. Caoses 5, 6, 7, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 28, 29, 30, 32.

12. Cases 10, 22, 25, 26, 27, 31.

13. Cases 5, 6, 7, 13, 14, 15, 16, 17, 18, 19, 20, 21, 23, 24, 28, 30, 32.

14. Cases 10, 12, 22, 25, 26, 27, 29, 31.

obtained. By referring to Table 2 and the acidity curves, it will be observed (1) that of the fourteen meals eight showed decreased acid values at the end of an hour, the decrease being marked in most cases and corresponding with the change noted in the daily meal series; (2) that in some cases the acidity reached its height earlier with the oil meals, but that in half of the cases the height of the secretion with the oil meals is markedly delayed as compared with the controls; (3) that the secretion period, or the period of digestion, is distinctly prolonged in eight of the fourteen meals.

There are many factors associated with experiments of this character which render it almost impossible to duplicate at all times the observations on the phenomena of digestion which may be made on dogs with isolated miniature stomachs. The psychic effects are altogether of an opposing nature, and the method of experimentation of necessity is radically inferior. The dog knows nothing about his miniature stomach and has only the most pleasurable psychic influences during his feeding, digestion and subsequent experimentation. In our cases the knowledge of experimentation and the discomfort caused by the presence of the tube in the stomach, or by its frequent passing, are constantly present. Under such conditions there are certainly no appetizing influences at work and consequently little or no psychic juice, which seems to figure so largely in Pawlow's experiments, is secreted.

When, under ideal conditions, the administration of oil to dogs with miniature stomachs brings about lowered acidity values, delay of the height of digestion, lengthening of the digestive period and lowering of motility, and when experiments on the human stomach are followed, in a large proportion of cases, by results which closely simulate other dogs, it would seem only logical to conclude that the conditions observed in the dog's stomach are closely analogous to those which occur under similar conditions in the human being.

Such results as were obtained in Case 6 and Case 9 are influenced by a factor which in the one case (6) was not always at work, while in the other (9) it was constant, namely, the factor of hypersecretion. In the former case our examinations showed intermittent hypersecretion; in the latter continual hypersecretion, for in this case the fasting stomach always contained a strongly active gastric juice.

Our experiments show that, when once the secretion is induced, its progress is not easily influenced by oil. At times, in hypersecretion, even though the precaution be taken to wash and drain the stomach, only a few seconds will suffice to enable one to collect a sample of gastric juice of decided peptic value (Case 6). If, on the other hand, the fasting stomach contains no gastric juice and oil be introduced, the characteristic

group of digestive phenomena are almost invariably observed, namely, delayed secretion, retardation of the appearance of the height of digestion, prolongation of the digestive period.

DISCUSSION.

We have definitely confirmed the observations of others and proved that oil produces a certain group of gastric phenomena which are spoken of as depressant. The question as to how this is brought about appears to us to have been unsettled up to the present time. As cited in our introductory remarks, Pawlow maintains that the influence of fats and oils is exercised through reflex central stimulation of the inhibitory nerves of the glands or the inhibitory centers of these nerves; that it is not the result of their purely mechanical action in covering the mucous membrane and preventing excitation of the nerve endings. Later he admits that the mechanical effect has not yet been satisfactorily shown. Pawlow's experiments are conclusive that oil does have a central inhibitory action. But, we think, the purely mechanical effect of oil plays a great, if not as great, a part in lowering the acidity of peptic digestion.

It has long been known that certain kinds of food remain in the stomach longer than others, and that the evacuation of the stomach, as well as its secretion, is subject to food stimulation. If food, coated with oil, cannot stimulate the gastric nerve endings, no juice will flow until, by mechanical effect, the oil is removed from certain portions of the food. We may then consider that oil acts mechanically in two ways: (1) by covering the food; and (2) by covering the mucosa. We bring forward two experiments which seem to sustain these views. If three pieces of coagulated egg albumin of the same size be immersed for a few minutes in water, glycerin and olive oil, respectively, and then placed separately in tubes containing equal amounts of stomach fluid and incubated at body temperature, it will be observed that by the time the control has been completely dissolved, which occurs with comparative rapidity, the glycerinized piece is about one-half digested, while the piece immersed in oil is only beginning to show the slightest change around the edges. It is quite apparent from this experiment that oil interferes with digestion by coating the food and mechanically preventing the digestive juices from attacking it.

The fact that oil, given immediately before or after a test meal, does not bring about so marked a lowering of the secretions as when it is given half an hour before, leads one to believe that there are more than reflex central inhibitory influences at work. Food stimulation, as well as psychic stimulation of nervous mechanisms, is usually more

promptly induced. Two ounces of olive oil administered ten minutes before a meal depresses the secretion more than does one ounce, but not as much as when it is given thirty minutes before the meal.

To see if this mechanical phenomenon could be shown graphically, the following experiment was conducted in the Radiographic Department of the University Hospital. Our thanks are due Mr. Vernon J. Willey, director of the laboratory, for giving freely of his time, and for the excellent radiographs made.

Two ounces of olive oil, intimately mixed with one ounce of bismuth subnitrate, were given to a very thin patient with slight gastroptosis. The patient was strapped to a plate and two minutes after swallowing the mixture an exposure was made. Another plate was exposed at ten minutes, another at fifteen, and still another at twenty-five minutes. In the first plate the oil and bismuth appears as a roundish or oval mass lying at the bottom of the stomach. As the time progressed an increase in the area of coating occurred, until at twenty-five minutes the entire stomach was coated.

From this experiment, particularly when taken in conjunction with Case 8 and the preceding experiment, it can be asserted that olive oil delays the secretion of the gastric juice to a considerable extent, at least by mechanically coating the walls of the stomach.

Taking all facts into consideration, the following conclusions appear to be justified:

1. Oil depresses the secretions of the stomach by reflex central action.

2. The reflex action is unlike that of ordinary food stimulation in that it is slower.

3. The reflex central action is a quantitative one, the depression becoming greater as the amount of oil administered is increased.

4. Oil depresses the secretion of the gastric glands by mechanical inhibition of food stimulation: (a) by coating the food; (b) by coating the stomach wall.

5. In proportion to the rapidity with which the walls of the stomach are covered with oil, the inhibition of secretion occurs, from nervous as well as from mechanical influences.

Our experiments lead us to the opinion that the characteristic group of phenomena which follow the administration of olive and cotton seed oil are due to mechanical action as well as to reflex, central, inhibitory stimulation.

Much knowledge can be obtained from experiments of this character. Such experiments, though laborious and beset with numerous factors of error, are entirely feasible. Although the results compare closely with

those acquired by animal experimentation, still it would seem advisable to proceed along some such line as this and investigate the action of all food stuffs, as well as of such drugs as are supposed to influence gastric secretion. A trustworthy control and a suitable subject are the all-important requirements. In the University Hospital cases hyperchlorhydria was present. In the Craig Colony cases the secretions were for the greater part within what we call the normal limits. Normal cases would probably form a more ideal basis of investigation from a purely experimental point of view.

CONCLUSIONS.

1. Olive oil and cotton seed oil, when given in connection with the usual test breakfast, decrease the gastric acidity at the end of the hour and retard the evacuation of the stomach.

2. The beginning of the secretion of hydrochloric acid is delayed when oil precedes the meal, unchanged when oil follows the meal.

3. The height of digestion is delayed when oil is given either before or after the meal.

4. The height of secretion is lowered when oil precedes the meal, unchanged when oil follows the meal.

5. If the progress of digestion is watched by the removal of small samples of stomach fluid at frequent intervals it will be observed, when oil precedes the meal by one-half hour, that at the end of what is usually taken as the digestive period for a test breakfast (three-fourths to one hour) the acidity is distinctly lower, while as great a height as is present in the control meal is frequently reached some minutes later.

6. The action of oil on the stomach functions is only a temporary one. It has no effect on subsequent meals unaccompanied by oil.

7. The therapeutic value of oil is apparent. In *suitable* cases it is preferable to antacids because of its caloric value. In hyperchlorhydria it should precede the meal. In hypochlorhydria it should follow the meal. In stasis and persistent slow evacuation it should be eschewed. In hypermotility it may be given before, during or after the meal.

8. Oil lowers the gastric secretion both by reflex central inhibitory stimulation and by mechanical action.

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EXPERIMENTAL AND CLINICAL INVESTIGATION OF THE PULSE AND BLOOD PRESSURE CHANGES IN AORTIC INSUFFICIENCY.*

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INTRODUCTION.

Although the collapsing pulse has, since the time of Corrigan, been one of the most characteristic features of aortic insufficiency, and although in its exaggerated form it furnishes the most typical of all pulse tracings, nevertheless one is struck by the frequency with which the sphygmograph produces a seemingly normal tracing in cases of perfectly definite aortic insufficiency where the sensation to the finger is that of a collapsing pulse. Usually it has been considered that such tracings are the result of instrumental defect or imperfect technic in making the tracings, and in a few cases they are ascribed to a simultaneous occurrence of aortic stenosis along with the insufficiency.

The discrepancy between the sphygmographic tracings and the subjective notes is well exemplified in the examination of the records of patients observed in the Johns Hopkins Hospital during the past four years, in which the pulse was described and the description accompanied by a sphygmographic tracing. Of 50 such records of cases of aortic insufficiency, in 58 per cent. the pulse was stated to be collapsing, while in the remaining 42 per cent. it was described as being gradual in its fall or non-collapsing.

The large proportion of cases which do not present a collapsing pulse is a point of great importance, and will be referred to later. The rapidity of the upstroke, which is constantly referred to by authorities as one of the leading features of the pulse, varied so little in the various tracings that it was impossible to utilize it as a standard whereby the two types of pulses could be compared. Advantage was taken, however, of that other characteristic of the sphygmogram, viz.: the low position of the dicrotic notch on the catacrotic limb as the criterion for comparison. In all but two cases, in which the pulse was described as non-collapsing, the notch was situated above a line drawn parallel to the abscissa, and midway between it and the apex. In those cases described as collapsing,

* Thesis presented for the degree of M.D. of the University of Edinburgh, April 31, 1907. Awarded gold medal and authorized for publication.

no such definite relation existed, for in those in which the amplitude of the pulse wave was great it was situated below this line, while in those in which the pulse wave was small it assumed a position above it, and the tracing partook of all the characters of a normal pulse.

Examples of these different types of pulse in aortic insufficiency are seen in Figures 1, 2 and 3.

Fig. 1.—Pulse described as non-collapsing. The dicrotic notch is situated above the line midway between apex and trough of the waves. Case of uncomplicated insufficiency. Systolic blood pressure, 160. Diastolic blood pressure, 70.

From the explanation hitherto advanced, that collapse of the pulse in this disease results from regurgitation, it is difficult and indeed impossible to account for the absence of the collapsing pulse in the large percentage of cases mentioned above. The explanation which would first suggest itself would be that the leak was small in degree and insufficient to render the vessels flaccid. The intensity of the diastolic murmur at the base of the heart, or the extent of cardiac hypertrophy and dilatation being no absolute gauge of the amount of blood which regurgitates

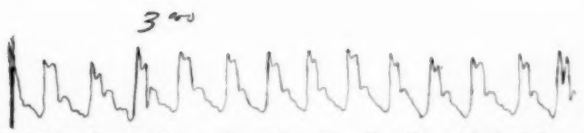

Fig. 2.—Pulse described as collapsing. The dicrotic notch is below the midline. Systolic pressure = 150. Diastolic pressure = 60.

into the ventricle, it was only from those cases which came to autopsy that information could be gathered on this point. Of the 21 cases which during life presented evidence of aortic insufficiency without a water-hammer pulse, 6 were examined postmortem. Four had varying degrees of arteriosclerosis. In 3 autopsies, the cusps were not so described that conclusions could be reached as to their actual incompetency. In the other 3, however, the valves were stated to be markedly shrunken and incompetent (without any accompanying stenosis). It is clear, then,

from these facts that distinct inadequacy of the aortic valves can exist without any accompanying water-hammer pulse, and its absence must be due to some other condition of the circulation.

The explanation will be proved experimentally to be that which was surmised by Sansom.[1] He recognized two types of pulse in aortic insufficiency. One in which the rise and fall are sudden, and a second in which there is "a resemblance with the tracings indicating high tension." In describing the latter class, he says: "The summit of the trace is broadened, the tidal wave being sustained, the dicrotic notch, though ill pronounced, is high in the tracing, and the gradually sloping line corresponding to the diastolic period tells of peripheral obstruction." The question, then, naturally arises, When shall a pulse be considered collapsing? Simple as this question at first sight seems, we are confronted at once with some difficulty in answering it. For, according to MacKenzie[2] and Broadbent,[3] the most distinctive feature of a collapsing

Fig. 3.—Pulse described as collapsing. The amplitude is small and the dicrotic notch is situated above the midline. Apparently a normal pulse tracing. Systolic pressure = 110. Diastolic pressure = 60.

pulse is, in effect, the fact that while in the normal radial pulse the dicrotic notch falls nearer the summit than the trough of the pulse wave (i. e., above the line drawn midway between summit and trough), in the collapsing pulse it is to be found below this line. In other words, the greater portion of the fall in the collapsing pulse occurs before the dicrotic notch, while in the normal pulse it occurs after it. Now, since Huerthle[4] has proved that the dicrotic notch divides the pulse tracings into two portions, the systolic occurring before the notch and the diastolic occurring after it, it is but a paraphrase to restate the criterion of MacKenzie and Broadbent by saying that *in the normal pulse the greater portion of the fall in the pulse wave is diastolic in time, while in the collapsing pulse of aortic insufficiency the greater portion of the collapse* (occurring before the dicrotic notch) *is systolic.*

1. Diagnosis of Diseases of Heart, London, 1881, p. 290.
2. Study of Pulse.
3. The Pulse, p. 205.
4. Arch. f. d. ges. Physiol., Bonn, 1891, xlix, 65.

In other words, if MacKenzie and Broadbent are correct, the greater part of the collapse occurs, not at the time when blood should be leaking back into the ventricle, but while it is still flowing from the ventricle into the aorta, during systole. The authors themselves do not attempt to explain this paradox; in fact, they do not even appear to realize its existence.

We are, therefore, confronted with the following problems:

First.—To investigate the substantial truth of the statement of MacKenzie and Broadbent, that the dicrotic notch occupies a low position in the pulse curve of aortic insufficiency. In other words, to determine whether the main fall of pressure is systolic or diastolic in time.

Second.—To determine the condition to which the main fall of pressure in aortic insufficiency is due.

In order to solve these problems, I have made numerous observations on patients in the medical service of Prof. L. F. Barker, in the Johns Hopkins Hospital, Baltimore, and I have performed many experiments on animals in the physiologic laboratory of the Johns Hopkins medical clinic, which is under the charge of Dr. A. D. Hirschfelder.

I would take this opportunity of expressing my warm thanks to Professor Barker for the many privileges which he has in so generous a manner extended to me while attending the medical clinic of the Johns Hopkins Hospital. Through his kindness I was enabled to utilize the clinical material under his charge and at the same time to carry on experimental work in the physiologic laboratory of his clinic.

I am also under a debt of gratitude to Dr. Hirschfelder. The experimental part of this research was carried out under his guidance, and my obligations are heartily acknowledged for the untiring assistance and valuable advice which he has at all times given me.

HISTORICAL SUMMARY.

While to Hodgkin[5] may be ascribed the distinction of being the first to give a clinical description of this disease, it was reserved for Corrigan[6] to offer, three years later, in 1832, an explanation of its most prominent features.

He recognized in the pulse only the grosser qualities of throbbing and pulsation. In his original article the following description is given:

"When the semilunar valves . . . become incapable of closing the mouth of the aorta, then, after each contraction of the ventricle, a portion of the blood just sent into the aorta, greater or less according to the

5. London Med. Gaz., 1829, iii, 433.
6. Edinb. Med. and Surg. Jour., 1832, xxxvii, 225.

degree of inadequacy of the valves, returns back into the ventricle. Hence, the ascending aorta and arteries arising from it, pouring back a portion of their contained blood, become, after each contraction of the ventricle, flaccid or lessened in their diameter. While they are in this state the ventricle again contracts and impels quickly into these vessels a quantity of blood which suddenly and greatly dilates them. The diastole of the vessels is thus marked by so sudden and so great an increase of size as to present the visible pulsation which constitutes one of the signs of the disease."

Corrigan was conscious of the fact that the backward current of blood could not sufficiently account for the appearance of the collapse in the arteries of the lower limb, or of the arm when dependent, since the blood would have to flow upward in its return to the aorta, and to render this possible he says: "The elasticity of the brachial arteries on the blood just urged into them forces it back along the retrograde current of the subclavians, no obstacle meeting it in that direction." He considered that the strength of the heart had little to do with the result, and that the explanation lay in the wave of large amplitude which was thrown into the empty artery.

Galabin,[7] forty years later, laid stress on the quality of extreme suddenness in the commencement of the pulse, which gives to the finger the sensation of a sudden jar or knock. He considered that this is the diagnostic quality of the pulse wave of aortic insufficiency, and pointed out that the amplitude of the wave itself is not characteristic, unless it is accompanied by the sudden jar.

This suddenness he attributed, not to an increased rate of systolic output, but to conditions in the vessel which altered the character of the pulse wave as it travels from the heart to the periphery. He maintained that the collapse did not exist in the larger arteries, such as the aorta and subclavian, but that the transformation which is seen in the wave as it traverses the peripheral vessels, is only an exaggeration of a change in the pulse form which takes place in the healthy adult. He showed that the rate of transmission of the pulse wave is dependent on the tension of the arterial walls, it being greater as the tension rises. Since the tension on the arterial walls is greater at the summit than at the trough of the pulse wave, the apex tends to overtake the base. The result is that the systolic elevation becomes steeper the further the wave travels from the heart. According to Galabin, in the normal pulse this tendency toward increased steepness of the systolic elevation is counter-

7. Trans. Roy. Med. and Surg. Soc., London, 1876, lix, 361.

acted by the recoil of the arterial walls, and as the influence which tends to make this upstroke steeper is the difference between the systolic and diastolic pressures, the conditions are established in aortic insufficiency for its production.

However faulty Galabin may have been in his reasoning, there is no doubt that he has the credit of being among the first to emphasize those qualities which we now imply with reference to the waterhammer pulse. These are the sudden, abrupt rise of the pulse curve and its rapid subsidence.

Clifford Albutt[8] introduces a new factor into the conditions which cooperate in the production of the collapsing or water-hammer pulse. The great changes of pressure which occur between systole and diastole have the effect of lengthening and widening the vessel, so that the walls adapt themselves but loosely to the blood which they contain. The arteries are thrown into curves, which on being straightened by each ventricular systole cause the vessel to be thrown out of its bed "with a visible and palpable jerk." That this contributes to the sensation of a jar or shock is undoubted, but it can not be the sole cause, for the water-hammer pulse can be distinctly seen before the vessels have had time to elongate, as is seen to follow the recent rupture of an aortic cusp.

With the exceptions already stated, our conceptions regarding the collapsing pulse have undergone no fundamental change since the publication of Corrigan's article, and while the blood pressure changes have been extensively studied in experimental aortic insufficiency by Cohnheim,[9] Romberg and Hasenfeld,[10] Kornfeld[11] and Rosenbach,[12] the underlying factors in the production of the collapsing pulse either are not mentioned by them or are assumed to be the direct consequence of regurgitation.

Among clinicians, some of the more recent authorities incline more to the emptiness of the arteries as the essential factor in its production (Gibson[13]), while others maintain that the sudden drop of the pulse wave is due to the loss of support from defective valves (Mackenzie[2]). The pervading idea is that the collapse occurs in the diastolic phase of the cardiac cycle, and that it is a direct consequence of regurgitation into the ventricle.

That the collapse is not diastolic, but occurs during ventricular sys-

8. System of Med., vi, 937.
9. Lect. on Clin. Path., New Syd. Soc., 1889, i, 49.
10. Arch. f. Exp. Path. u. Pharmakol, Leipz., xxxix, 333.
11. Ztschr., f. klin. Med., Berl., xxix, 91.
12. Arch. f. Exp. Path. u. Pharmakol., Leipz., ix, 1.
13. Diseases of Heart and Aorta, 183.

tole, and that it is only a secondary accompaniment of regurgitation, the evidence here advanced will prove.

METHODS OF INVESTIGATION.

The experimental part of this research was performed on dogs. It was found, after the first few experiments were performed, that the most suitable animal was a medium-sized English terrier, if possible over 2 years old. Young dogs were unsatisfactory, in that they did not appear to possess the same resistance as the older dogs and succumbed early in the experiment, owing to the severity of the cutting operation.

Each animal received ½ grain of morphia before being anesthetized with ether. This was administered by means of a tracheal cannula in connection with an ordinary ether bottle. After the thorax was opened, this was attached to an artificial respiration pump, and by the suitable adjustment of valve and T-tubes the lungs could be filled to any desired extent.

Fig. 4.—Dawson's maximal and minimal valves.

The pulse wave was recorded with a Huerthle membrane manometer, attached to the right carotid artery. Fling of the lever was eliminated by damping the movement with the screw lock of the apparatus.

The systolic and diastolic pressures were measured by the use of the maximal and minimal valves devised by Dawson[14] (Fig. 4). The more minute details are shown in Figure 5.

Each consists of two glass tubes, one enclosed within the other. The orifice of the inner tube, which is situated laterally, is surrounded by a layer of peritoneal membrane, so arranged as to permit the flow of fluid from within outward. When the inner tube A is attached to the artery, and the outer B to a mercury manometer, as in the upper figure, the systolic or maximal pressure only is recorded, the pressure in the outer tube being maintained by the membrane which closes the orifice C of the inner tube, when the pressure falls during diastole. By connecting the

14. Amer. Jour. of Physiol., Boston, 1906, xv, 224.

tube B with the artery and A with the manometer, the valve measures the minimal or diastolic pressure. The systolic rise of pressure now closes the orifice C, while the diastolic fall makes the pressure in the outer tube less than that which is in the inner, and thus causes a flow of fluid from the manometer toward the artery. By a suitable arrangement of stop-cocks (see photograph), the maximal valve is first connected with the artery, and having read off the systolic pressure on the manometer, it is cut off and the minimal or diastolic valve brought into communication with the artery.

In order to render the tracings less complicated, the systolic and diastolic pressures were read off and not recorded on the drum. It is to be noted that these valves do not record the systolic and diastolic pressures

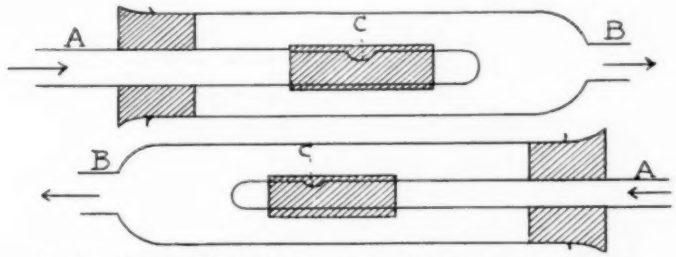

Fig. 5.—Minute details of Dawson's maximal and minimal valves.

of individual pulse waves. They measure the highest and the lowest pressures which have obtained in a given interval of time. If, however, this interval of time is made as short as possible, they will give records, which, for all practical purposes, are the systolic and diastolic pressures of the beats which occurred while the reading was being taken.

The amount of systolic output and the different phases of the cardiac cycle were recorded by the ventricular plethysmograph devised by Henderson[15] (Fig. 6).

It consists essentially of an ordinary soft rubber ball into which a circular window is cut, having a diameter of seven-tenths that of the ball. Over this window a very thin rubber dam is cemented with rubber cement, and after this has dried thoroughly a second circular window is cut into the rubber dam, this window having six-tenths the diameter of the window in the ball. A small hole is then cut into the side of the rubber ball, and through it a small glass tube is inserted and held in place with washers of cork or rubber. The apex of the heart is then

15. Amer. Jour of Phys., 1906, xvi, 325.

inserted into the window in the dam, and the plethysmograph pushed over the heart until the rubber dam fits about the auriculoventricular groove. The fitting should be airtight, but never sufficient to compress the heart. As Henderson states, it is necessary to have several sizes of the plethysmograph, and balls of diameters of 7, 9 and 11 cm., respectively, were used, according to the size of the heart. By its opposite end the plethysmograph communicates by rubber tubing with a large Marey tambour. The superiority of this instrument over that of Roy and Adami and the older forms lies in the fact that it registers the volume changes of the ventricles only, and, the transmission being by air, the ventricles are subjected to no external pressure which would impede their diastole.

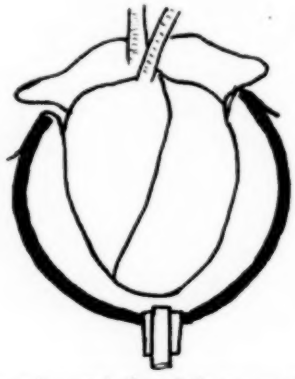

Fig. 6.—Henderson's ventricular plethysmograph in position.

After each experiment, the tambour was calibrated by attaching it to the upper end of a graduated burette filled with water. One cubic centimeter of water was run out at each time, and the excursion of the lever recorded.

After the insertion of the tracheal cannula, the internal mammary arteries were ligatured in order to avoid hemorrhage when the chest was opened. This was done by prolonging the incision for the preliminary tracheotomy to the upper border of the sternum, and separating the suprasternal muscles. The pleuræ were then punctured by the finger and, having dissected the arteries with the finger, a ligature was passed around them with an aneurism needle and then the ligatures tied.

The heart was exposed by reflecting the skin and pectoral muscles by a median incision extending along the whole anterior aspect of the chest. The ribs were cut near their attachments to the cartilages, and the ster-

num and costal cartilages removed. The pericardium was incised and reflected, and the plethysmograph slipped over the ventricles, until the rubber membrane grasped the auriculoventricular groove.

The aortic valves were ruptured by MacCallum's valvulotome.[16] This instrument (Fig. 7) consists of a steel cutting hook which is passed down the left carotid artery. The cutting surface is on the concave

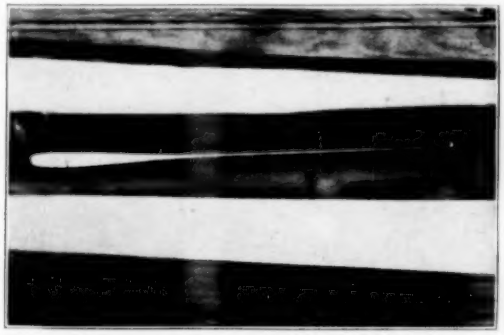

Fig. 7.—MacCallum's valvulotome.

aspect of the hook, which is so curved that it does not injure the vessels when passed down toward the heart. The instrument is pushed down the artery until it enters one of the sinuses of Valsalva, after which it is forced through the base of the cusp. The hook is then pushed inward, and, on being withdrawn, it cuts the cusp in two.

Intraventricular pressure was measured by means of a metal catheter passed down the left carotid artery and connected with a Huerthle manometer (Fig. 8).

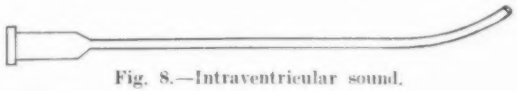

Fig. 8.—Intraventricular sound.

The changes in auricular pressure were recorded by passing a glass cannula into the auricle through a pulmonary vein and connecting this with a Harvard membrane manometer.

For the arterial, intraventricular and auricular pressures, the medium of transmission was a 5 per cent. solution of sodium citrate.

The heart of the animal was examined at the termination of each experiment, and only in those cases in which the valves were torn were

16. Johns Hopkins Hosp. Bull., Balt., No. 185, 1906.

the results put on record. In several cases, it was found that, in addition to the production of insufficiency, the intraventricular septum and the chordæ tendinæ were injured. The results of these experiments were not taken into account. In all, thirty experiments were performed, of which ten were successful, i. e., the aortic valves only being injured. In 9 the myocardium had been more or less damaged. In the remainder no insufficiency was obtained.

Methods of Recording.—Simultaneous tracings were made of the pulse changes, the volume changes of the ventricles, and of the time in fifths of a second with a Jacquet chronograph. In the earlier experiments smoked paper was employed, but in the later ones, by the use of improved writing pens, it was found that black on white tracings were

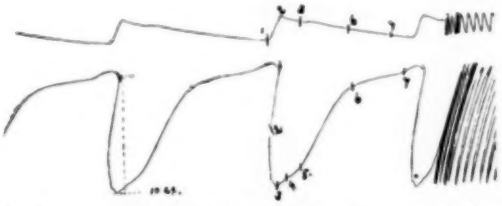

Fig. 9.—Simultaneous tracing of the pressure in the carotid artery (upper curve) and of the volume changes in the ventricle (lower curve): 1. Commencement of ventricular contraction. 2. Summit of primary wave. It is reached about the time that the ventricle has discharged half its contents into the aorta. 3. End of systole. It corresponds to the dicrotic notch in the carotid tracing. 3-4. The rapid increase in volume due to the filling of the coronary arteries. 5. End of relaxation or diastole proper. 6-7. Period of diastasis. 7. Commencement of auricular systole. The contraction of the auricle takes place after the ventricles have practically filled. It causes only a slight rise in ventricular volume. The downstroke 1-3 indicates a systolic discharge of 10 c.c.

more satisfactory. In every case, before and after a tracing was taken, the maximum and minimum blood pressures were read off. Typical normal tracings were always obtained before the aortic valves were injured.

THE VENTRICULAR VOLUME CURVES OF THE NORMAL HEART.

The results obtained by Henderson[13] are of such far-reaching importance that they mark a new era in our conceptions regarding the mechanism of the circulation in the normal heart. And, if true of the normal heart, they must modify to a still greater extent our views concerning the changes which occur in the circulation as a result of incompetency of the aortic valves. As one of the main arguments of this research is based on these results, his experiments have been carefully repeated, and the findings are in entire accord with those which he has obtained.

Figure 9 is a simultaneous record of the volume curve and the lateral pressure in the aorta as measured from the right carotid artery. After making allowance for the time taken by the pulse wave to reach the carotid artery, the figures represent simultaneous events in the two tracings. It will be seen that the greater part of the downstroke of the volume curve is practically a straight line, indicating a uniform rate of systolic discharge. Keeping in view the fact that the lever carrying the pen writes in the arc of a circle, the lower part of the systolic downstroke is seen to be more gradual, showing that toward the end of systole the discharge is less rapid; 3 indicates the end of systole and the commencement of ventricular relaxation. This is seen to correspond with the dicrotic notch of the carotid tracing. Immediately following the completion of systole there is a small, rapid rise of pressure from 3 to 4.

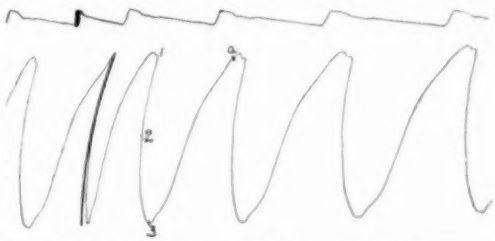

Fig. 10.—Simultaneous tracing of carotid pressure (upper curve) and of volume curve of normal ventricle (lower curve). The heart rate is increased to the optimum rate. The period of diastasis is abolished and the auricular systole (a) follows immediately the ventricular relaxation. The filling is complete. Systolic output, 12 c.c.

Henderson believes that this is due to the rapid entrance of blood into the coronary vessels after they are released from the compression of the contracted ventricles. For an instant after this sudden rise of pressure there is a delay from 4 to 5, followed by a large upstroke *which is almost as rapid as the systolic discharge.* The tracing shows the ventricles have filled at 6 in .43 of a second, early in diastole, and they remain in this quiescent state until the onset of the following auricular systole. At 7 the auricle contracts, and it is seen that it ejects only a fraction of a cubic centimeter of blood into the already filled ventricle.

RELATION OF HEART RATE TO THE AMOUNT OF SYSTOLIC OUTPUT.

While the preceding tracing may be taken as typical of the heart beating at a normal rate, Figure 10 shows the changes which occur when the rate of the heart beat is increased. Tracing No. 25 shows, after

vagal stimulation, the effect of a slowing of the heart. It will be seen that at the higher rate the rate of discharge or refilling has not appreciably varied. The change has involved only a shortening, and in this case abolition of the period of quiescence. On the other hand, after vagal stimulation, the duration of systole and relaxation have remained the same, but slowing has been affected by lengthening the interval of rest. It is evident that an increase of rate up to the point which abolishes the period of quiescence increases the amount of blood thrown out into the aorta, per unit of time, and, other things being equal, it will increase the work done by the heart and also the mean pressure in the arterial system.

If, however, the heart be made to beat at a still higher rate (Fig. 11), the relaxation curve is encroached on by the following systole and, complete filling being prevented, it will involve a diminution in the amount of blood discharged at that systole. The work done by the heart in such

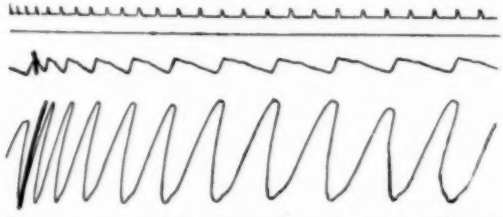

Fig. 11.—Upper curve, carotid pressure. Lower curve, volume curve of ventricle. This shows effect of a very fast heart rate. Not only is there no period of diastasis, but the ventricular filling is interfered with by the following systole. The output at each contraction is diminished. Systolic discharge, 8 c.c. Time in fifths of a second.

a case is not increased, for, although the rate is greater, the amount thrown out at each systole is less, and, therefore, the output per unit of time does not vary.

The conclusions, then, which are to be drawn from the volume curves of the ventricles are:

First.—That the part played by the systole of the auricles is of little importance in the filling of the ventricles. They act more as elastic reservoirs than as muscular force pumps. The force which fills the ventricle is acquired from the potential energy stored in the walls of the auricles from their distension by the venous pressure. The ventricles are not filled by the contraction of the auricles, for they are already full before the onset of auricular systole. Henderson thinks that the wave of increased pressure sent into the ventricles by the auricular systole has as its function only the closure of the auriculoventricular valves, which have previously been floated into position by the inflow during diastole.

Second.—That the rapidity of ventricular relaxation is independent of the rate of the heart, and is an unalterable characteristic for each heart.

Third.—That the cardiac cycle is not diaphasic but triphasic, and "consists of systole, the period of contraction and discharge, diastole the period of relaxation and filling; diastasis, the period of rest."

EFFECT OF VOLUME CURVES OF VENTRICLES WHEN AORTIC VALVES ARE DAMAGED.

The most satisfactory method of comparing the volume curves before and after insufficiency is to trace the normal on transparent paper and lay this over the abnormal. It is necessary for this purpose that the heart rate be the same in the two tracings and the rate of rotation of the drum

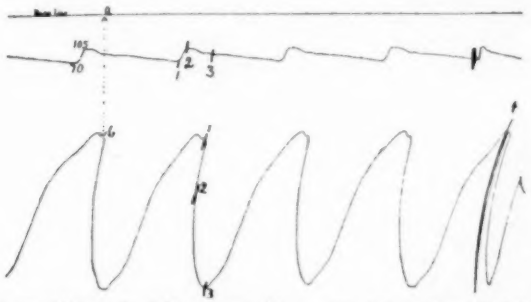

Fig. 12.—Carotid and plethysmographic curves taken immediately before the production of insufficiency. Systolic pressure, 105; diastolic pressure, 70; systolic output, 12.8 cc. The line a-b represents the ventricular tonus.

constant. Figures 12 and 13 are the actual tracings taken before and after the production of insufficiency.

When the tracings are superimposed (Fig. 14) it will be seen, contrary to expectation, that the rapidity of ventricular output is slower in aortic insufficiency than it is normally. This is proved by the fact that the apex of the curve is reached in the normal in .18 second, while in the abnormal it occupies an interval of .22 second.

The amount of ventricular output differs in the two by only ½ c.c. of blood. This is in direct contrast to the views at present held regarding regurgitation. It is thought that the amount of blood which returns to the ventricle when added to that which normally enters from the auricle is sufficient to cause a dilatation of the ventricles. Even with the most extensive damage to the valves, the increased systolic output did not exceed the normal by more than 1 c.c. of blood.

The upstroke, that part of the tracing which represents the cardiac filling, shows that the ventricle fills somewhat faster in the abnormal condition. Its acceleration, however, involves only the commencement of diastole proper, as is demonstrated by the more gradual ascent of the first part of the uprise. After the ventricles have filled to about one-fifth of their capacity, the rate of filling becomes the same, the remaining part of the uprise being gradual. When the heart remains the same, the time lost by the longer systole is compensated for by this increased rate of filling in early diastole.

If, now, the distance between the diastolic positions of the curves and the base line be compared in the two tracings, an indication will be

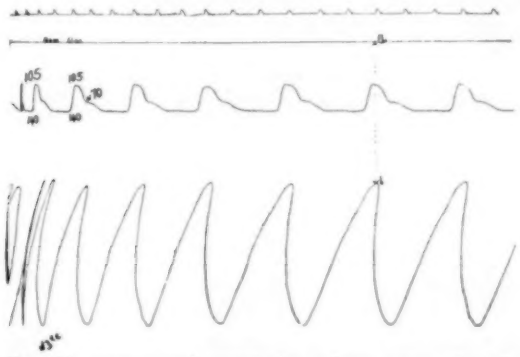

Fig. 13.—Carotid pressure and ventricular volume curve after the production of aortic insufficiency. Systolic pressure, 105; diastolic pressure, 40; systolic output, 13 c.c. The line a-b represents the ventricular tonus. Compare with tracing No. 12, in which it is shorter. This indicates that the ventricle is less distended. Ventricular tone and distension vary inversely with one another.

given of the relative distension in the two conditions. The "base" in this instance being situated above the tracing, it is, of course, evident that the shorter this distance the greater the ventricular distension, and *vice versa*. On the other hand, the further the systolic portions of the curves are from the base line the more completely do the ventricles empty themselves.

It must be recalled that the systolic discharge volume of the normal heart is not necessarily an indication of the amount of ventricular distension or of the actual amount of blood which the ventricle contains. As Henderson[17] has shown, it is about 60 per cent. of the total volume difference between extreme distension as would follow a prolonged vagus

17. Loc. cit., p. 365.

stimulation and extreme contraction, as exhibited in hearts which have stopped beating in systole.

A constant systolic discharge may be obtained in one of three ways. (1) It may occur with the normal amount of relaxation and the normal degree of ventricular contraction. (2) With an increased relaxation and less complete ventricular contraction, the residual blood being increased. (3) With a diminished relaxation and a more complete systole, in which case the residual blood is diminished.

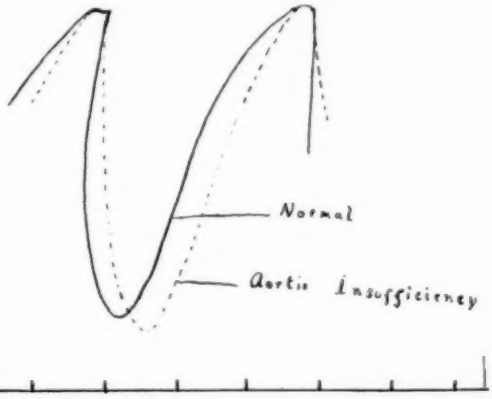

Fig. 14.—Superimposed tracing of the normal ventricle and that of the ventricle after the production of aortic insufficiency. The rate of systolic discharge is slower in abnormal state.

These different states of the ventricle are represented diagrammatically in Figure 15. As to which of these three conditions will obtain will depend entirely on the ventricular tonus. A comparison of this distance in the two tracings (12 and 13) reveals the surprising fact that the production of aortic insufficiency causes the ventricle to contract in Condition 3, viz.: with a diminished relaxation and more complete systole. The amount of residual blood which is known to exist normally is diminished, and, while the ventricular filling is slightly greater, the ventricle at the end of diastole is less distended. This is also shown in Figure 18.

It is impossible, in view of these facts, to accept the statement of Johannsen and Tigerstedt,[18] that in experimental aortic insufficiency the ventricle does not empty itself so completely. This statement was based chiefly on the theoretic grounds that when the ventricular cavity is dilated the blood is less completely expelled during systole. But it has

18. Skand. Arch. f. Physiol., i, 331.

been shown above that the ventricle is less distended after the simple production of aortic insufficiency, and this can only result from an increased ventricular tonus. It will be shown later that if the tone is diminished the ventricle dilates and the amount of residual blood becomes increased. The comparison of the tracings, however, furnishes important information on the quantity of blood which regurgitates. In the animal from which these tracings were taken the posterior cusp was completely divided by MacCallum's valvulotome, and a greater degree of insufficiency thus produced than can probably occur in man as a

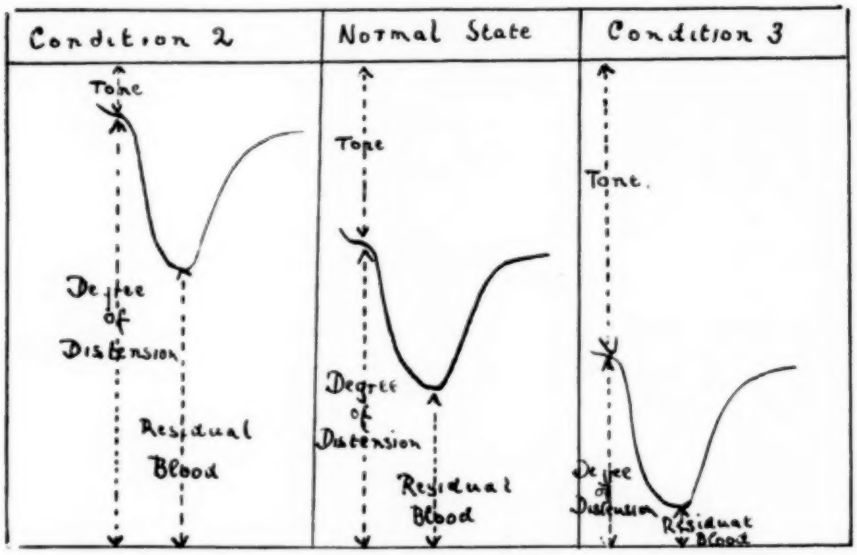

Fig. 15.—Diagram to illustrate the different conditions under which the ventricle with intact valves may contract. The curves represent a plethysmogram, indicating the same amount of systolic discharge in the three conditions. The length of the interrupted lines indicates the degree of tonus, the degree of distension and the amount of residual blood, respectively. In Condition 2 there is an increased relaxation and an increased amount of residual blood, but a diminution of the degree of tonus. In Condition 3 the tonus is increased, while the degree of distension and the amount of residual blood are diminished. Tonus varies inversely with distension and the amount of residual blood.

result of disease. As stated above, the systolic output in the two cases, at the same pulse rate, differed only by ½ c.c. of blood. There was no diminution in the amount of blood delivered by the auricle, as was evidenced by the fact that there was no dilatation of its cavity.

The facts admit of but one interpretation, viz.: that after an extensive valvular lesion the actual amount of blood which regurgitates is fractional in quantity as compared with that which enters naturally from the auricle.

It may, then, be asked why the loss of so small a quantity of blood should give rise to the various phenomena associated with this lesion. The point will at once become clear when one understands that the essential change is a loss of pressure rather than a transference of blood from the aorta to the ventricle. It must, of course, be admitted that some blood must regurgitate, but the conditions under which the regurgitation occurs, are such that it becomes of the smallest possible amount. The aorta and ventricle being in direct communication, the pressures in the two chambers will tend to become equalized, and the curves of intraventricular and arterial pressures will show that this does occur. But a transference of pressure does not necessarily presuppose a transference of blood, just as a rise of pressure in the radial artery during the passage of the pulse wave is not due to a corresponding increase in the amount of the radial blood stream.

The tendency toward regurgitation is lessened in the first place by the low pressure which will be shown to obtain in the aorta immediately after the completion of systole. This systolic end pressure or that which is present at the termination of the systolic plateau will be shown, also, to be very different from that which is produced at the summit of the primary wave, and the relation of the two is an indication of the rapidity of capillary flow. It is entirely distinct, although it does not differ, on an average, by more than 15 mm. mercury from the pressure in the aorta at the end of diastole. The difference in pressure between the systolic end pressure and that at the end of diastole is accounted for partly by the loss due to regurgitation and partly by the capillary escape. Under no circumstances, then, can this fall of pressure due to regurgitation exceed or even equal this difference.

But another factor contributes to the prevention of a large amount of regurgitation of blood, viz.: the rapidity of ventricular filling. At the moment of ventricular relaxation, the pressure in the left ventricle is negative, and, as a result, the aortic and auricular blood are rapidly forced toward the ventricle. But since, as has been shown already, in the physiologic condition the ventricle receives venous blood only during the early part of diastole, the outflow from the auricle must take place with extreme rapidity. In the pathologic condition, while the difference between the pressures in the left auricle and the aorta is still great, and would increase the rapidity of stream from the latter, the great differ-

ence in size between the two openings through which the blood enters will render the amount of blood delivered from the aorta insignificant as compared with that which comes from the auricle. The ventricles will have filled, therefore, before an appreciable quantity has returned from the aorta. And since the volume curves show that the ventricular tone is greater, immediately the filling is completed, the ventricles are able to withstand the relatively low pressure which is transmitted from the aorta without becoming further distended. When the intraventricular pressure curves are presented, it will be seen that at the end of ventricular repletion the pressure has already reached that which obtains in the aorta, and during the period of diastasis there is no further increase of intraventricular pressure.

The change in form which results in the volume curve as a consequence of increased tension at once suggests an analogy with the corresponding effect of tension in the contraction of a skeletal muscle. The

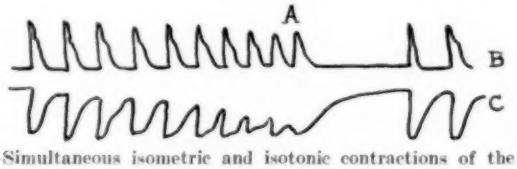

Fig. 16.—Simultaneous isometric and isotonic contractions of the frog's gastrocnemius.

similarity, which was first referred to by Francois Franck[19] between the volume curve and the isotonic muscular contraction and between the intraventricular pressure curve and an isometric contraction in the normal heart, was subjected to experimental test by Henderson.[20] By means of an apparatus called a work adder he was able to cause a skeletal muscle (a frog's gastrocnemius) to record simultaneously an isometric and an isotonic curve. In an isometric contraction the muscle is made to contract against a resistance which it is unable to overcome. The resistance commonly employed is a strong spring, and the small excursion induced is greatly magnified by the use of levers. The shortening which results in the muscle being negligible, the curve indicates the changes in tension which the muscle undergoes. An isotonic contraction, on the other hand, is one in which the muscle is, or is not, loaded with a weight which it is able to lift, and the natural shortening is not impeded. The isometric curve is distinguished from the isotonic by the more rapid uprise, indicating that the greatest tension is reached much sooner than

19. Trav. du lab., de Marey, 1877, iii, 321.
20. Loc. cit., p. 357.

the greatest shortening, and by an apex which is flat topped instead of rounded. Henderson's simultaneous isometric and isotonic curves (Fig. 16) show in a striking manner the close resemblance which they bear, respectively, to the pressure and volume curves of the normal ventricle.

As a skeletal muscle is influenced in the form and strength of its contraction by changes in the tension which precede or accompany its contraction, so also is the heart when increased tension is thrown on it, as a consequence of abnormal states. Starling[21] holds that in the normal state the ventricle contracts isotonically, since after overcoming the aortic pressure the muscle fibers can shorten without further hindrance, while in aortic stenosis the ventricle meets with resistance during the whole period of its systole, and, therefore, approximates an isometric contraction. In aortic insufficiency, however, we have a condition in which the increased tension is exerted before the onset of the ventricular contraction and is comparable to the "loaded" isotonic curve. The normal volume curve is similar to the "after-loaded muscular contraction," that is to say,

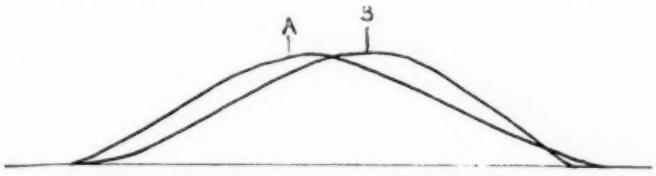

Fig. 17.—A. After-loaded contraction. B. Loaded contraction.

the tension to which the muscle is subjected is that of the load, and it begins to act only after the muscle has already contracted. The ventricles are subjected to no tension before contracting, and, after reaching a certain degree of contraction, the tension remains constant until the end of systole. It is different, however, when the aortic values are incompetent. Here a considerable tension exists in the ventricular walls as a consequence of the transmission of pressure from the aorta. The condition is the same as that which exists in a loaded muscle preparation, tension is applied to the muscle before it contracts. A comparison of the two volume curves at once shows their resemblance to an after-loaded and a loaded muscle, respectively.

The inversion of the volume curve will render the resemblance still more striking. The above curve (Fig. 17) is based on the work of von Kries[22] and shows the effect of applying tension to a muscle prepara-

21. London Lancet, 1897, i, 570.
22. Arch. f. Physiol., Leipz., 1880, p. 370.

tion before contraction. The uprise is more gradual, showing that the rate of contraction is diminished, and the summit of the loaded curve follows that of the after-loaded muscle. It will be recalled that the volume curve of the ventricle in aortic insufficiency differs from the normal in exactly the same respects. It was shown that the rate of ventricular output is slower, and the time taken to effect complete systole delayed.

But the comparison may be extended further. The ventricular contraction of the normal heart is analogous to that in a muscle which contracts and at the summit of its contraction is relieved of its load and allowed to relax without any extending force. The heart in aortic insufficiency, however, is comparable to the muscle which is subjected to ten-

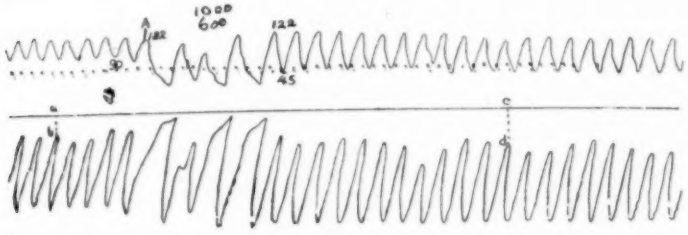

Fig. 18.—Carotid pressure and ventricular volume curve to show the effect of the production of aortic insufficiency. (a) Equals insufficiency produced. The systolic pressure remains the same, 122 mm. of Hg., but the diastolic pressure falls from 90 mm. Hg. to 45 mm. Hg. The volume curve shows that for four beats after the production of the lesion the ventricle becomes considerably dilated, and at this moment regurgitation does probably occur. After a lapse of about two seconds, however, the ventricle recovers itself and the distension becomes less afterward than before. The line c-d is longer than a-b, equals increase in the ventricular tone. The ventricle also empties itself more completely. The apex of the volume curve is further from the base line.

sion during the phases of contraction, elongation and rest. The effect of tension so applied is to increase the rapidity of elongation, and to this action we may attribute the more rapid uprise of its volume curve. The conclusion arrived at by Schenck[23] in relation to the effect of tension on the contraction of skeletal muscle may with equal force be applied to the ventricle: "Tension protracts contraction and hastens relaxation."

EFFECT ON BLOOD PRESSURE OF RUPTURE OF THE AORTIC VALVES.

Cohnheim,[9] in his classical experiments, found that, although the valves are ruptured and no longer able to effect closure during diastole, "the mean arterial pressure remains at precisely the same level." Rosenbach[12] repeated his experiments and obtained the same results. Since then

23. Arch. f. d. ges. Physiol., Bonn, 1894, lvii, 606.

the investigation has been undertaken by numerous other observers, but their experiments do not, in every case, agree with those of Cohnheim and Rosenbach. While MacCallum[10] found that the blood pressure remains remarkably high, Kornfeld[11] noticed that it may either be increased or diminished.

These experimenters, without exception, used the ordinary mercury manometer attached to the carotid artery. As is well known, this instrument does not follow promptly the quick changes of pressure which occur between systole and diastole, and the limited excursion gives only an approximate reading of the mean blood pressure; nor, on account of its relatively sluggish movement, can either the systolic or diastolic pressures be accurately measured. The use of the Huerthle manometer, along with the maximal and minimal valves, gives a ready means whereby both systolic and diastolic pressures can not only be measured accurately, but also recorded.

The following table gives the result of the production of aortic insufficiency on the maximal and minimal blood pressures in ten experiments:

Expt.	Before.		After insufficiency.			
No.	Sys.	Dias.	Sys.	Dias.	Lesion.	Result.
1	125	90	125	50	Post. cusp.	Dog survived shock of lesion.
2	126	80	90	20	Int. cusp.	Dog died.
3	140	120	140	30	Post. cusp large.	Dog survived.
4	115	80	115	28	Ext. cusp.	Dog survived.
5	105	70	75	35	Post. cusp.	Dog died.
6	170	155	100	40	Post. cusp.	Dog died.
7	100	70	100	45	Post. cusp.	Dog survived.
8	155	120	160	80	Ext. cusp.	Dog survived.
9	150	72	150	50	Post. cusp.	Dog survived.
10	120	90	85	10	Post. cusp.	Dog died.

It will be seen that in none is the systolic pressure increased after the valves are rendered incompetent. In those cases in which the animals survived the shock of the lesion, the *systolic pressure remained at exactly the same level.* The diastolic pressure invariably undergoes a diminution which was found not to depend entirely on the amount of damage done to the valves. While the systolic pressure is not affected by the lesion, the mean pressure falls, since, as shown by Dawson,[24] it is nearer and follows the diastolic pressure much more closely than the systolic. In all the experiments, therefore, the mean blood pressure fell. It is to be noted that in those animals which succumbed after the production of the insufficiency the systolic pressure also underwent a marked diminution. This merely indicated that the heart was failing and unable to eject the previous quantity of blood. The ventricles under these cir-

24. Ref. Erlanger and Hooker, Johns Hopkins Hosp. Rep., 1904, xii, 150.

cumstances gradually dilated and stopped beating in diastole after the lapse of about ten minutes. And while the fall of systolic pressure resulted from a lessened output the maintenance of the systolic pressure showed that the amount of systolic output in the non-hypertrophied and non-dilated heart did not vary. This was also shown by the volume curves of the ventricles after damage to the aortic valves.

In the meantime it is to be emphasized that the mean blood pressure falls considerably, and this fall is proportional to the fall in the diastolic pressure, the systolic pressure remaining the same as before.

Fig. 19.—Carotid tracing to show the effect of rupture of the aortic valves. Systolic pressure 150 mm. Hg. before and after the lesion. Diastolic pressure falls from 70 to 50 mm. Hg.

It was frequently observed in the earlier experiments that when the valvulotome failed to enter the sinus of Valsalva, but passed directly into the ventricle without damaging a valve, the curve assumed the form seen in undoubted insufficiency. There was an immediate fall in blood pressure, with a great increase in the pulse pressure. Indeed, on two separate occasions the collapsing character of the pulse which resulted was so marked that it was assumed that a valve was cut, and the experiment was proceeded with without again introducing the instrument. When,

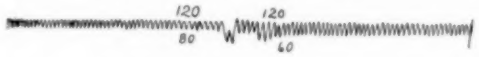

Fig. 20.—Carotid tracing showing the fall in diastolic pressure from irritation of the posterior wall of the ventricle by the valvulotome. There was no insufficiency produced. Systolic pressure before and after, 120 mm. Hg.; diastolic pressure before, 80 mm. Hg.; diastolic pressure after, 60 mm. Hg.; slow drum.

however, the heart was examined postmortem, one was astonished to find that the valves were absolutely intact. In a third experiment it was thought that an insufficiency was obtained, but after the lapse of about an hour the collapsing character of the pulse disappeared and, in view of the previous experience, it was suspected that the instrument had merely entered the ventricle without damaging the valves. It was again introduced and the external cusp torn, which was found on autopsy to be the only valve damaged. The tracings of these experiments are shown in Figures 20 and 21.

In seeking for an explanation of this phenomenon one was at first inclined to believe that it was due to the presence of the instrument in the mouth of the aorta which prevented closure of the valves. This, however, could not have been the cause, since the collapse persisted after the withdrawal of the instrument.

It seems not at all unlikely that the rubbing of the point of the instrument on the posterior wall of the ventricle mechanically stimulated the endings of the depressor nerve and thus brought about the immediate fall in blood pressure. This hypothesis seems justifiable, in view of the fact that Köster and Tschermak[25] showed anatomically that the nerve ends partly in the wall of the ventricle and partly in the aorta beyond its mouth. Whatever the explanation is, the observation has an important bearing on the question of the collapsing pulse. It proves that this type of pulse is not peculiar to aortic insufficiency, but can be obtained in any condition in which, with a persistence of ventricular activity, there is a fall in the diastolic blood pressure.

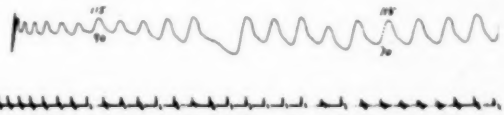

Fig. 21.—Carotid tracing to show also the fall in diastolic pressure which results from passage of the valvulotome into the ventricle without damaging a valve. Diastolic pressure fell from 90 to 70 mm. Hg. No change in systolic pressure.

COMPARISON OF THE NORMAL PULSE WITH THAT OBTAINED AFTER PRODUCTION OF AORTIC INSUFFICIENCY.

Huerthle[4] has shown, and the plethysmographic tracing confirms it, that the period which elapses between the appearance of the primary and the dicrotic wave is an accurate measure of the outflow from the heart during systole. Of course, it is evident that it is not synchronous with the commencement and termination of systole, since a fraction of a second elapses before the ventricle gathers sufficient strength to open the semilunar valves, and a definite interval also elapses after the end of systole before the appearance of the dicrotic waves. Huerthle found, however, that these intervals are of the same length; therefore, all changes occurring between those points are included in the systolic phase of the pulse curve.

Since the abnormal condition induced by the rupture of the aortic valve does not affect the mechanism of the production of the systolic

25. Arch. f. d. ges. Physiol., Bonn, 1902, xciv, 24.

portion of the pulse curve, that phase can be compared, point by point, in the two pulses. While in the pulse of aortic insufficiency the diastolic portion is the product of an abnormal mechanism, the systolic in both is affected physiologically.

The Amplitude of the Ascending Limb of the Pulse Wave.—The production of aortic insufficiency invariably increases the pulse pressure. The following table shows the increase which took place in six experiments:

Expt.	Before insufficiency.			After insufficiency.		
No.	Sys.	Dias.	Pulse pressure.	Sys.	Dias.	Pulse pressure.
1	125	90	35	125	50	75
2	140	120	20	140	30	110
3	115	80	35	115	28	87
4	100	70	30	100	45	55
5	155	120	35	160	80	80
6	150	72	78	150	50	100

According to Marey,[26] it was first demonstrated by Hales, and afterward by Bernard, that when the blood pressure falls, the amplitude of the pulse is increased. Marey himself confirmed their observations, and more recently the investigation has been revised by Huerthle[27] with improved methods. He showed that the fall of blood pressure resulting from stimulation of the depressor nerve is accompanied by an increase of the pulse pressure, and conversely that the rise of blood pressure from splanchnic stimulation diminishes the pulse pressure.

Granted, then, a constant systolic output, vasodilation will increase the pulse pressure by lowering, while vasocontraction will diminish it by raising the diastolic blood pressure.

But the pulse pressure is materially influenced by the amount of blood ejected at each ventricular systole and by the relative capacity of the arterial tree. Different amounts of blood, thrown into an arterial system whose capacity does not vary, will produce differences in pulse pressure which will be greater the larger the systolic output. The difference will be affected by an increase of the maximum pressure rather than by a lowering of the mean or diastolic pressure.

If, then, after the production of aortic insufficiency increase of the pulse pressure be accompanied by an increased systolic pressure, the diastolic remaining the same, it must have resulted from an increased systolic output. If the diastolic pressure is lowered and the systolic pressure remains as before, there must have been an attendant vasodila-

26. La Circulation du Sang., p. 269.
27. Pflueger's Arch., 1888, xxxiv, 393.

tion. If, on the other hand, the increased pulse pressure is the result of a lowering of the diastolic and an increase of the systolic pressure, it must have been caused by a true regurgitation. The regurgitated blood will have been added to the normal systolic output, thus raising the maximum pressure, while the diastolic pressure will have been lowered by the loss of the same amount.

The actual conditions which obtain in experimental aortic insufficiency have already been shown (page 123). It was shown that when the animal survives the production of the lesion, the systolic pressure remains at exactly the same level, whereas the diastolic pressure falls in a very marked manner. The pulse pressure has been increased because of this fall, and, as above stated, it can only have resulted from peripheral dilatation.

The Systolic Plateau.—That portion of the pulse curve which extends from the point of maximum pressure to the commencement of the dicrotic notch has been termed by Marey the systolic plateau. This plateau may be horizontal, ascending or, as in the normal pulse, descending.

Fig. 22.—After Marey.

When it is horizontal the inflow of blood is exactly equal to the systolic escape from the capillaries. When it ascends, as in the anacrotic pulse, the escape is less than that received into the arterial system, and the pressure continues to rise. When it descends the indication is that the systolic escape by the capillaries is greater than the systolic influx. It naturally follows that the steeper the declivity of the systolic plateau, the greater is the excess of the systolic escape over the systolic inflow. Such, for instance, can always be seen to take place in the normal pulse when the capillary flow is accelerated from dilatation of the peripheral arterioles by the administration of nitrate of amyl.

The comparison of the normal pulse with that obtained after the production of aortic insufficiency shows the much greater systolic fall of the latter. Indeed, the main fall of pressure is composed of this declivity, for the amount of fall which is purely diastolic, viz., from the dicrotic notch to the abscissa, is almost negligible, as compared to that which occurs in systole.

It must be conceded, then, that from the form of the pulse curve alone we have evidence that the essential feature of the collapsing pulse lies in the systolic phase of the cardiac cycle. The pulse differs in no way from that in which, with the maintenance of ventricular activity, there is a relaxation of the peripheral resistance.

EFFECT OF CHANGES IN HEART RATE IN AORTIC INSUFFICIENCY.

From the examination of the volume curves of the normal heart it was shown that an increase of rate up to a certain limit increased the amount of systolic output per unit of time. The action is due to the shortening of the period of diastasis, which allows of an increase of heart rate, without interfering with the ventricular filling. Erlanger[28] and Hooker observed that an increase in the quantity of blood thrown out in a given time will increase the mean and therefore the diastolic pressure in the arterial system. In aortic insufficiency an increase in the diastolic blood pressure must increase the pressure which is transmitted to the ventricular walls during diastole. Any increase of rate, however, beyond that which abolishes the period of diastasis occurs at the expense of diastole, in Henderson's sense (i. e., time of filling), for each succeeding systole will take place before the normal relaxation of the ventricle is completed. The blood thrown out during systole must, then, be diminished, and while the heart beats more rapidly, the output in a given time does not vary. The diastolic pressure will, therefore, undergo no further augmentation.

Disregarding for the time being the possible influence which a lengthening of the period of diastole and diastasis may have on regurgitation, it is evident that in so far as aortic pressure is affected by changes in rate a slowing of the pulse within normal limits will not affect the pressure which can be transmitted to the ventricle, whereas an undue lengthening will lower it. Regarded in this light, an unusually slow heart rate is advantageous in aortic insufficiency.

This effect of rate, however, becomes secondary to that which it has on regurgitation and transmission of pressure. It is usually taught that a lengthening of the period of diastole is disadvantageous in that it increases the leak into the ventricle and causes it to dilate. This is clearly based on the conception that an "appreciable" quantity of blood returns to the ventricle. It has been shown in the plethysmographic records that the volume of the blood which regurgitates in experimental insufficiency is negligible, and that the phenomena associated with the

28. Johns Hopkins Hosp. Rep., 1904, xii, 160.

condition are due to the attendant transmission of pressure. An estimation, then, of the rate at which this pressure is transmitted will give the desired information as to whether a lengthening of the period of diastole and diastasis is harmful or advantageous. For, clearly, if the pressure in the ventricle equals that in the aorta at the end of ventricular relaxation, it is immaterial how long the period of diastasis may be, since it will involve no further increase of the intraventricular pressure. If the pressure, on the other hand, is transmitted slowly from the aorta to the ventricle; that is, if the intraventricular pressure rises gradually during the whole period of diastole and diastasis and equals the aortic pressure just before the following systole, then a lengthening of the period of diastasis will have a harmful effect.

In order to determine which of these conditions holds in aortic insufficiency the curve of intraventricular pressure was recorded in three experiments.

Fig. 23.—Intraventricular pressure tracing from the normal ventricle. Contrast with tracing No. 24.

Figure 24 is the intraventricular pressure curve after the posterior aortic cusp was divided. It shows a somewhat oblique upstroke, which corresponds closely to the protracted volume curve of systolic discharge. The systolic plateau is rounded and merges insensibly into the diastolic downfall. The fall in pressure is at first rapid, but it becomes more gradual as it approaches the abscissa. This latter point is of great importance, for it stands in marked contrast with the abrupt and uniform fall in pressure which is seen in the intraventricular pressure curve of the normal heart, as in Figure 23.

It will be recalled that the plethysmographic records showed that the effect of aortic insufficiency was to increase the tonus of the ventricle, and, as a consequence, its distension during diastole was less than in the normal heart. It was shown also that the increased rapidity of filling took place only during the first fifth ventricular relaxation. This of itself would indicate that at the end of this period, viz., the first fifth of relaxation, a certain amount of aortic pressure had already been transmitted to the ventricle, and its further relaxation was effected with an increasing tension on its walls. As is well known, the pressure in

the normal ventricle falls below atmospheric pressure immediately after the ventricle begins to relax, as a consequence of the suction action exerted by its walls. If, as in aortic insufficiency, a positive pressure is being transmitted at the same time from the aorta, it should follow that this fall in pressure will become less rapid, and the downstroke of the intraventricular curve more inclined. That such is really the case, tracing No. 24 proves.

On the one hand, the relaxation of the ventricle tends to produce a diminution of the pressure within it, while, on the other hand, the free communication with the aorta will permit of the transmission of positive pressure. The excess (algebraically) of the negative over the positive will occasion a fall of the intraventricular pressure curve, which will be slow or rapid according as the excess is small or great. In other words, if the aortic diastolic pressure is high, and the communication between it and the ventricle large, the fall in pressure in the latter, during its relaxation, will be more gradual than if the leak were small or absent. Further, it is evident that the fall will be more rapid at the begin-

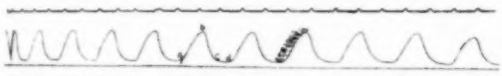

Fig. 24.—Intraventricular pressure curve after production of aortic insufficiency. The upstroke a-b is more gradual, as is also the fall in pressure b-c. The line c-d is horizontal, showing that the intraventricular pressure does not rise during the period of diastasis. The figures represent the pressure in mm. of Hg. at different points of the curve.

ning of the process of equalization than near its termination, since then the negative relaxation pressure in the ventricle is greatest. The rate of fall, therefore, is seen to be more gradual as the downstroke reaches the abscissa, for the negative pressure is being gradually neutralized by the positive.

The most striking feature, however, of the curve of intraventricular pressure lies in the fact that the downstroke does not reach the abscissa at any stage of the diastolic phase. Following the gradual fall of pressure which accompanies the completion of ventricular relaxation, the lever traces a line which runs parallel to the abscissa, and in this instance indicates a pressure of 40 mm. Hg. But the rapidity with which the aortic pressure is transmitted to the ventricle varies directly with the size of the communication. It follows, therefore, that when the insufficiency is extensive, the pressures in the aorta and ventricle become equalized during the period of relaxation, and there is no further transmission in the phase of ventricular diastasis. This proves conclusively

that, under such circumstances, if the tonus of the ventricle is maintained a slowing of the heart rate can not have a harmful influence in aortic insufficiency.

It is possible, however, in those cases in which the opening between the aorta and ventricle is small that the delay in the transmission of aortic pressure which results may cause the pressure in the ventricle to rise during the whole period of diastole. The smallness of the communication probably accounts for the rise of diastolic pressure seen in the tracings of Marey.[29]

He produced an aortic insufficiency in the horse by the passage of a cardiac sound which merely punctured an aortic cusp. An insufficiency thus produced is much smaller than that which follows section of the cusp. Further, it was noticed in the present series of experiments that an opening in a valve produced by the cardiac sound becomes blocked

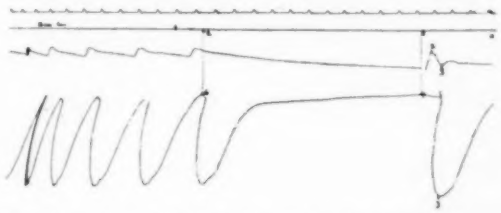

Fig. 25.—Carotid and ventricular volume tracings from the normal heart, showing the effect of vagal stimulation. The difference between the lines a-b and x-y represents the distension of the ventricle due to loss of tone = 1 c.c. of blood. Stimulation of the nerve slows the heart rate by prolonging the period of diastasis. The rapidity of ventricular filling is not affected. The marks on the base line indicate the period of stimulation.

rapidly by the formation of a fibrin clot. In one such experiment a clot had formed in an hour, and many of the features of this condition became distinctly less marked.

A gradual rise of pressure, then, is possible when the communication is small, and only under such circumstances can a slowing of the pulse rate, *per se*, be said to have a harmful influence on the ventricle. A similar conclusion as to the effect of rate is arrived at from the results obtained by stimulation of the peripheral end of the vagus nerve.

EFFECT OF VAGUS STIMULATION.

The effect of the stimulation of this nerve has purposely been omitted from the discussion of the relation of heart rate to aortic in-

29. Loc cit., 674.

sufficiency, since stimulation of the vagus gives rise to two (among several) distinct physiologic changes in the ventricle.

As is well known, when the peripheral end of the vagus is stimulated, in addition to slowing of the ventricular contraction, it diminishes ventricular tone. The two effects can not be disassociated, and, while at first we would appear to have a ready means of studying the effect of rate on regurgitation, we are immediately confronted with the difficulty that arises as a result of the diminution of tone, simultaneously induced.

When the vagus is stimulated the volume curve of the normal heart shows that the ventricle becomes gradually distended (Fig. 25). This follows from the fact that the auricular pressure, although small, is sufficient to overcome the diminished tone of the ventricular walls.

If after aortic insufficiency has been produced the nerve is stimulated with the same strength of current and for the same length of time, any distension which may take place beyond that which occurs normally

Fig. 26.—Carotid and ventricular volume tracings after the production of aortic insufficiency. The vagus nerve was stimulated at A and the loss of tone causes the ventricle to dilate. The amount of distension produced (difference between a-b and x-y) is the same as in the normal heart—1 c.c. in each. The slowing of the heart rate, therefore, can not allow of regurgitation of blood.

under vagus stimulation will result from regurgitation. In this manner only is it possible to draw any accurate conclusions as to the effect produced by slowing the heart rate experimentally by vagus stimulation.

In order to confirm the findings obtained by the records of the intraventricular pressure curves, two such tracings are reproduced. In the normal, Figure 25, the effect is seen to involve only the period of diastasis. The vagus standstill allows the completion of diastole, which is completed in the usual time, in this case .272 of a second. The line of prolonged diastasis inclines gradually upward, and indicates a distension of the ventricle from loss of tone.

Practically the same thing is seen to occur in tracing No. 26, where the aortic valves have been damaged and the distension which results

is no greater than that which occurs in the normal heart, 1 c.c. of blood in each.

Before stimulation the tone of the heart whose valves were damaged was greater than that of the normal, in consequence of the mechanical stimulation of increased intraventricular pressure. During stimulation the tone is reduced in both in the same degree, and a correspondingly equal distension is produced in the two states.

It is interesting to note that even after vagus stimulation the tone of the ventricle, when the aortic valves are damaged, as measured by the distance of the volume curve just before systole from the base line, is equal to that which obtains normally in the heart with intact valves.

This experiment has a twofold bearing. Taken in conjunction with the intraventricular pressure curves, it proves beyond doubt the relative unimportance of heart rate, *per se*, while, on the other hand, it emphasizes the important rôle which the ventricular tonus plays in the prevention of extreme regurgitation.

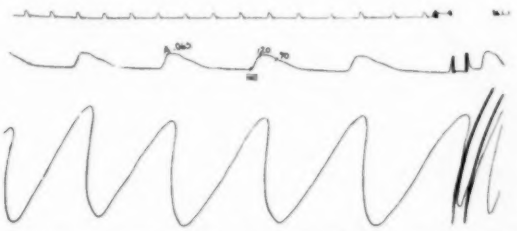

Fig. 27.—Carotid and ventricular volume curve in aortic insufficiency before compression of the abdominal aorta. A, summit of the primary wave. It is reached in .065 of a second after the commencement of systole. Systolic pressure, 120 mm. of Hg.; pressure at beginning of diastole, 70 mm. of Hg.; pressure at the end of diastole, 40 mm. of Hg.; systolic output, 12 c.c. (Compare with tracing No. 28.)

EFFECT OF INCREASING PERIPHERAL RESISTANCE.

The examination of the pulse of aortic insufficiency, and the similarity between the action of a true rupture of the aortic valves and an irritation of the ventricular wall in lowering blood pressure, have suggested the importance of a vaso-dilatation as the important factor in the causation of the collapsing pulse. It becomes necessary, then, to test experimentally the effect of changes in the peripheral resistance.

There are three methods by which it is possible to obtain varying degrees of increased resistance: (1) By stimulation of the splanchnic nerves; (2) by the injection of adrenalin; (3) by compressing the abdominal aorta.

While the first method in general is the most satisfactory, it was found that under the circumstances in which the records were obtained in this research it was impracticable. The dissection necessary to stimulate these nerves, following an already extensive cutting operation on the thorax and the production of a valvular lesion, was more than the animal was able to stand. It was necessary, then, to employ only the methods of abdominal compression and adrenalin injection.

If one accepts the dictum of Corrigan, that the collapsing pulse is due to the regurgitation of blood from the aorta, then any condition which retards the forward flow of blood must, of necessity, increase regurgitation, and thus render more pronounced the collapse of the pulse.

That the collapse is not increased by such a means, but entirely abolished, a glance at tracings Nos. 27 and 28 will show. They repre-

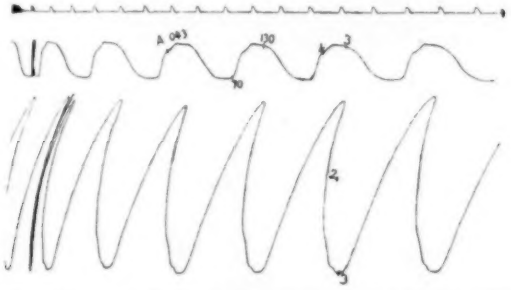

Fig. 28.—Carotid and ventricular volume curve of aortic insufficiency during compression of abdominal aorta. Note the change in the character of the pulse. A, summit of primary wave, is reached in .043 of a second after the commencement of systole. Systolic pressure, 130 mm. of Hg.; pressure at end of systole, 130 mm. of Hg.; pressure at end of diastole, 70 mm. of Hg.; systolic output, 13.5 c.c.

sent the changes in pulse form and volume curve which follow compression of the aorta at its bifurcation.

Change in the Pulse Form.—These curves show in a striking manner the truth of the statement of Marey regarding the conditions which modify the systolic portion of the pulse. There being a great disparity between the rate of inflow and the rate of outflow, the summit of the primary wave A is reached in a relatively shorter period during compression of the aorta. When the flow was unrestricted the time taken by the primary wave to attain its maximum was .065 second, while now it is reached in .043 second. The "systolic plateau," for the same reason, becomes ascending, and the dicrotic notch occupies the summit of the

curve. It will be seen to coincide exactly with the end of systole, as measured by the plethysmograph, .01 second in each.

The fall of pressure is now entirely diastolic, since the systolic plateau does not descend. The pressure which exists in the aorta at this moment is 130 mm. Hg., as contrasted with 70 mm. Hg. in the corresponding part of the ordinary curve of aortic insufficiency. There is thus established the ideal condition for regurgitation. Notwithstanding that the diastolic fall of pressure is more gradual than it is even in the normal tracing with intact valves, and only reaches the abscissa .06 second before the succeeding systole; *or,* in other words, the *conditions most favoring regurgitation caused the cessation of the collapsing quality in the pulse.*

Change in the Volume Curve.—The effect on the systolic contraction is merely an exaggeration of that which occurs in the ordinary state of insufficiency. The tension transmitted to the ventricular walls before contracting is greater, and the "loading" effect is more pronounced. The systolic contraction is still more protracted and the rate of systolic discharge slowed. It will be seen from the record that the diminished rate of output is more marked toward the end of systole, the tracing becoming more oblique as the apex is approached.

There is, however, this distinction. The tension is now so great that the tone of the ventricular wall is no longer able to counteract it, and a considerable regurgitation results. The distance from the base line at the end of diastole is shortened.

Further, so great is the resistance to be overcome in the aorta during the latter part of systole that the ventricle fails to effect so complete an emptying of its cavity. The difference in the quantity of residual blood is small, however, and does not amount to more than 2 c.c.

The record shows conclusively that regurgitation can not account for the collapsing pulse. Even with the increased systolic output and the greater pulse pressure, due to regurgitation, when the aorta is compressed, an increase of the resistance to onward flow of blood abolishes its collapsing character, and, conversely, a diminution of the resistance will exaggerate it, although this can not be tested experimentally, when the aortic valves are damaged, as the diastolic pressure is already reduced to a minimum. It is easy, however, to follow the successive changes in this type of pulse which result from the gradual relaxation of an increased resistance.

The position assumed by the dicrotic notch becomes gradually lower on the descending limbs of the pulse curve and the systolic plateau becomes first horizontal and then descending. This indicates a gradual

lowering of the pressure, which is transmitted to the ventricles at the commencement of their relaxation, since it is the pressure which exists in the aorta at the moment of closure of the aortic valves.

An increase of the rapidity of capillary escape, then, may be said to have a preservative influence on both the heart and the arterial system. It diminishes the magnitude of the pressure at the end of systole, and, therefore, prevents the transmission of high pressure to the ventricular walls during their relaxation. It also slows the rate of rise of the primary wave, and thus counteracts the tendency to dilatation of the arteries, as would be caused by the sudden stretching attending the passage of a steep wave of pressure.

The injection of adrenalin effects a change in the pulse curve which is identical with that of compression of the abdominal aorta. It raises the aortic pressure at the commencement of diastole, and, therefore, dis-

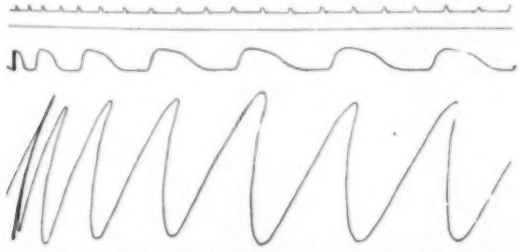

Fig. 29.—Carotid and ventricular volume curve of aortic insufficiency to show the effect of the injection of adrenalin. It is similar to that produced by compression of the abdominal aorta. Compare with the ordinary tracing of aortic insufficiency No. 27.

tends the ventricle by the regurgitation of blood. But the contraction of the peripheral arterioles retards the escape of blood through the capillaries, and the pulse ceases to be collapsing. On account of the stimulating action which it exercises on the ventricular contraction, the systole is more complete, and the effect it produces on the volume curve differs from that of abdominal compression in that the quantity of residual blood is diminished. Tracing No. 29 was taken on a fast drum when the drug had produced its maximum effect.

CLINICAL APPLICATION OF EXPERIMENTAL RESULTS.

The most important points which have been brought out from the experimental investigation of the pulse and blood pressure changes in aortic insufficiency are briefly:

1. That the so-called water-hammer pulse owes its abruptness and rapid fall not to regurgitation into the ventricle, but to an increased blood flow through the capillaries.

2. That this increased capillary flow is due, in a recent insufficiency, to reflex inhibition of the vasomotor center, probably induced by stimulation of the depressor nerve effected by the mechanical action of the pressure transmitted from the aorta.

3. This pressure simultaneously increases the ventricular tone.

4. That so long as the tonus is maintained a slowing of the pulse can not have any appreciably harmful influence on the amount of blood which regurgitates.

It becomes necessary, then, to apply these results to the aortic insufficiency which is due to disease, and to inquire as to how far they will help to explain the clinical discrepancies previously mentioned.

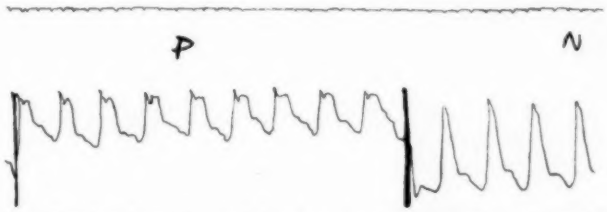

Fig. 30.—Tracing from the radial artery to show the effect of terminal constriction. P, during constriction. N, Tourniquet removed.

It is obvious that if the main fall of pressure is due to an increased rate of capillary flow it will follow that any condition which retards it should cause the disappearance of the collapse. This can readily be accomplished in the case of the radial artery by constricting the terminal vessels of the hand by the application of an elastic tourniquet. If a sphygmographic tracing be taken from a typical case of aortic insufficiency in the manner recommended by Lewis,[30] with weight instead of band fixation of the sphygmograph, the effect of decreasing the outflow from the artery will at once become apparent.

Such a tracing before and during terminal constriction is shown in Figure 30. The patient suffered from pure uncomplicated aortic insufficiency. He had a systolic blood pressure of 130 mm. Hg., and a diastolic blood pressure of 65 mm. Hg. and subjectively a typically collapsing pulse. The instrument used was a Jacquet chronosphygmograph. This instrument being a heavy one, it sufficed only to lay it over the artery

30. Jour. Physiol., Lond., 1906, xxxiv, 393.

without encircling the wrist with the usual sphygmograph band. The tourniquet was applied below the level of the thumb, well away from the sphygmograph, so that on being tightened the tracing could not be affected by the wrinkling of the skin. The contrast is striking. Before the terminal vessels are constricted the amplitude of the pulse is great, the apex of the wave pointed, and the systolic plateau is a steep decline. During constriction, on the other hand, the amplitude becomes small and the trough of the waves does not reach the abscissa, thus indicating an artery which does not empty itself. The systolic plateau is more horizontal, and the dicrotic notch assumes relatively and absolutely a higher position on the tracing. Indeed, the tracing so transformed is the counterpart in every detail of the tracings of aortic insufficiency which Sansom describes as "having a resemblance with the tracings indicating high tension."

A similar result, although in a totally different manner, has been obtained by diminishing the rapidity of capillary flow by the aid of venous constriction. As has been pointed out by Bayliss and Starling,[31]

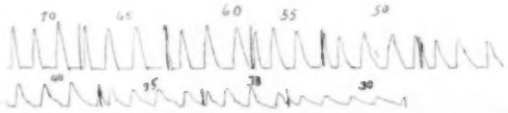

Fig. 31.—Series of tracings of the brachial artery taken with varying degrees of venous obstruction. When the pressure in the cuff is lower than the diastolic pressure the arterial inflow to the limb is not affected, while the venous return is restricted. The numbers indicate the different pressures in the cuff.

the capillary flow and pressure are greatly influenced by changes in the venous pressure, the flow being greatest when the pressure is least. If, by constricting the limb with a cuff bearing a pressure less than the diastolic blood pressure, the free inflow to the limb is not retarded, any desired amount of venous restriction may be obtained. A tracing, No. 31, from the branchial artery under such circumstances, is shown above. It will be seen that the collapse disappears and the catacrotic limb of the pulse curve becomes gradual in its fall.

So strong has been the stimulus of a dominant and preconceived idea that clinicians have sought to extend this idea into the explanation of many of the other attendant features of aortic insufficiency. Thus it is universally held that the reason why the collapse is more marked when the limb is elevated is due to the greater ease with which the blood can flow back into the ventricle. Apart from the physical impos-

31. Jour. Physiol., Lond., 1894, xvi, 157.

sibility of there being a retrograde blood current where there is a driving strength of even 50 mm. Hg., as indicated by the diastolic pressure, this view can readily be controverted by a simple experiment.

If, while the limb is elevated, the upper arm is encircled in a sphygmomanometer cuff, and the pressure raised to a point below diastolic pressure, so as to obstruct the venous return only, the intensified sensation of the collapse is now no longer felt. This experiment, while disproving the theory that the collapse is due to regurgitation, at the same time renders it evident that the elevation of the limb increases the sensation of the collapsing pulse, not by increasing backflow, but because it increases the capillary flow by hastening the venous return.

But the capillary pulsation so common in this condition is also ascribed directly to regurgitation. It is said that it is due to the empty condition of the peripheral vessels in diastole which results from regurgitation into the ventricle. In view of what has been said above, it is only necessary to quote an observation of Gibson's[32] while commenting

Fig. 32.—Apparently normal tracing from a case of aortic insufficiency which gave subjectively a collapsing pulse. The effect of an increase of systolic pressure is seen in tracing No. 34.

on this phenomenon: "It must be allowed that it may occur in conditions permitting a free passage of blood through the arterioles and capillaries into the veins." He further states that a direct venous pulse may develop in the peripheral veins, the pulsation following systole and passing from the periphery to the center.

Granted, then, that the collapsing pulse has its causation in the periphery and not in the center, the explanation of the clinical discrepancies previously mentioned becomes at once apparent. The collapsing pulse can exist only when the diastolic blood pressure is low, since when the systolic pressure remains constant the diastolic pressure is regulated by the rapidity of flow from the peripheral vessels. In other words, it is possible to receive the impression of a collapsing pulse only when the arterial walls are subjected to a slight distending force during the diastolic phase of the cardiac cycle.

32. Loc cit., p. 493.

It has, however, been frequently observed in those cases in which the diastolic pressure is low that when the systolic pressure is also low the pulse may give to the finger the impression of a sudden decline, while the sphygmograph tracing may show a more or less sustained pulse wave.

Tracing No. 32 is taken from such a case in which, with a systolic pressure of 75 mm. Hg. and a diastolic of 55 mm. Hg., the pulse felt typically collapsing. The patient, aged 20, suffered from aortic insufficiency, the result of acute rheumatism.

This discrepancy has its explanation in the fact that the pulse is not felt during the whole period of time in which the systolic wave is passing, and it is only that part of it which corresponds to the summit of the pulse wave that impresses itself on the finger. In order that a low pressure pulse, in which the pulse amplitude is small, may be palpated satisfactorily, the finger must be allowed to rest but lightly over the

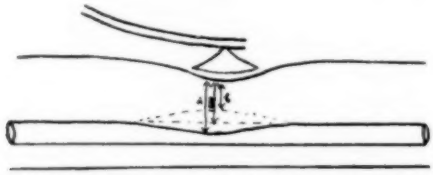

Fig. 33.—Diagram to illustrate the effect which different degrees of pressure exerted by the sphygmograph button will have on the excursion of the arterial wall during the passage of the pulse wave.

artery. There is, therefore, communicated to it only that part of the pulse which arises from the excursion of the arterial wall beyond its diastolic limit, i. e., the apex of the pulse wave. This is further evidenced by the fact long recognized by clinicians that if the wrist or forearm of a patient suffering from this disease be grasped lightly by the hand the water-hammer quality is much intensified. Under such circumstances the vessel, distended by the wave produced by the ventricular systole, is felt only at the summit of its distension. When, however, the sphygmograph records the largest amplitude of wave for a given pulse the pressure which is exerted by its pad is approximately equal to the pressure which obtains within the vessel.

During the interval between the pulse waves the arterial walls are somewhat approximated, as in Figure 33, and in this condition the systole of the ventricle will cause them to execute a greater movement. But, owing to the low diastolic pressure and to the fact that the pulse amplitude is small, the arterial wall is stretched but slightly. The arterial

recoil, therefore, will not be forcible, and it will return gradually to the position assumed during diastole.

The low systolic pressure in the patient mentioned above being an indication of a feebly contracting left ventricle, the effect of treatment was to raise it from 75 mm. Hg. to 105 mm. Hg., while the diastolic pressure remained as before, viz., 50 mm. Hg. The change resulting in the sphygmographic tracing is interesting, for it presented a fairly typical collapsing pulse, while at the same time it gave the collapsing sensation to the finger. This change in the character of the tracing can readily be explained by the greater stretching force to which the artery was subjected during the passage of the primary wave. Haycraft[33] has recently shown that within wide limits the arterial walls obey Hooke's law, which means that the amount of extension is proportional to the force which produces it. It follows, then, that the more the vessel is distended the more rapid will be the rate of recoil. It thus becomes evident how it is that the finger can always receive the sensation of a

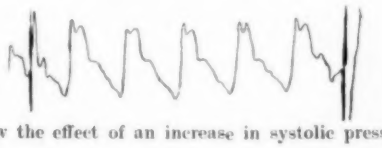

Fig. 34.—To show the effect of an increase in systolic pressure. The pulse is more collapsing.

collapsing pulse when the diastolic blood pressure is low, while it is only in those cases in which the pulse pressure is excessive that it can with certainty be recorded by the sphygmograph.

It is also easy to explain the absence of the collapsing pulse in the percentage of cases previously mentioned. These cases must have presented high diastolic pressures, although they are not recorded, since it is only within the last two years that we have been in a position to measure the diastolic pressure clinically. The high diastolic pressure in the majority of these cases was probably the result of the accompanying arteriosclerosis which most of the cases presented. It is to be noted, also, that the absence of the collapsing pulse need not be due to a small pulse pressure, i. e., the difference between systolic and diastolic pressure, or, conversely, a large pulse pressure need not necessarily be accompanied by a collapsing pulse.

A collapsing pulse can only be seen in those cases in which the diastolic blood pressure is low. The fact that a high diastolic blood pressure should cause the sphygmograph tracing to assume a gradually sloping

33. Jour. of Physiol., Lond., xxxi, 392.

line, even when there is a great range between the systolic and diastolic pressures, is due to a condition depending on the physical property of the arterial wall. Roy[34] showed that while Hooke's law is obeyed when the pressures are normal, when they are exceeded the extensibility of the artery rapidly diminishes.

From the figures given by Roy of the extensibility of the arterial walls at different pressures two pulse curves are drawn (Fig. 35).

In both instances the excess of systolic over diastolic pressure is the same, viz., 60 mm. Hg., but they differ in that the one, the diastolic pressure, is below normal, viz., 50 mm. Hg., while in the other it is somewhat above normal, viz., 80 mm. Hg. In the lower curve the amplitude is double that in the upper, the angle between the upstroke and downstroke is more acute and the dicrotic notch relatively lower. In the upper curve

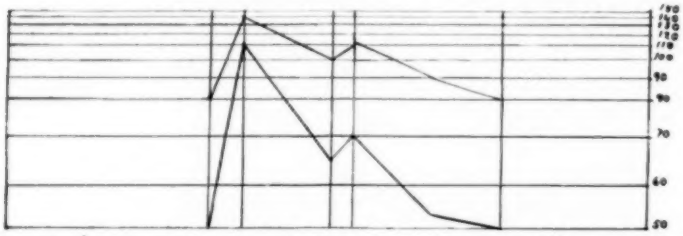

Fig. 35.—Diagrammatic representation of two pulse curves indicating the same pulse pressure, but at different diastolic pressures. The horizontal lines indicate the extensibility of the artery at given pressures (after Lewis).

upstroke and downstroke are oblique and the angle between them is widened.

In the curve taken at the low pressure there is more movement of the arterial wall for the same change of pressure. The one would be classified as a "collapsing" pulse, the other as "sustained."

THE LOW PERIPHERAL RESISTANCE IN AORTIC INSUFFICIENCY.

Starling[21] has pointed out that in disturbed conditions of the circulation the reflex mechanism called into play aims more at sparing the heart from overexertion than in counteracting the original vascular disorder. So in aortic insufficiency the function of a reflex dilatation of the peripheral vessels is a conservative one, being the method adopted by Nature to relieve the heart of the increased work thrown on it as a consequence of the transmission of pressure from aorta. This reflex action, however, is wholly distinct from that which occurs in old standing

34. Jour. of Physiol., Lond., 1881, iii, 135.

cases, which are due to disease, for now there are produced in the arterial system conditions which obviate the necessity of a continuous action on the part of the vaso-dilators.

The great changes in pressure between systole and diastole have the effect of stretching and widening the coats of the peripheral arterioles so that they remain permanently dilated. This dilation subserves the function of the reflex inhibition of the vasomotor center, which takes place after an experimental insufficiency. It was shown by Romberg and Hasenfeld[10] that several months after an insufficiency had been produced in rabbits the vasomotor nerves were less active than normal and the same degree of peripheral constriction could not be effected by their stimulation.

The question, then, immediately arises why the ventricle becomes hypertrophied and dilated to such an extraordinary extent, if an appreciable quantity of blood does not regurgitate, and the increased work thrown on the heart can be greatly obviated by a peripheral dilatation.

In order to make the point clear, certain properties of the contractility of muscle must be mentioned briefly. Haidenhain[35] has shown that when the tension on a skeletal muscle is increased before it contracts, the energy of the contraction becomes greatly augmented. The apex of a frog's heart ceases to beat under ordinary circumstances, but it can be made to contract by distending the cavity of the ventricle with fluid. Gaskell[36] also showed that after the apex of the frog's heart is rendered quiescent by crushing a ring of tissue above it, it can be made to contract again by clamping the aorta.

The excitory effect of increased tension in both cardiac and skeletal muscle is thus firmly established. Moreover, this mechanical effect involves a great expenditure of cardiac energy, for it is accompanied by an augmentation of all the chemical processes which accompany contraction, as is evidenced by the increase in heat production. In aortic insufficiency, instead of a pressure equal only to the atmospheric pressure as in the normal ventricle, the intraventricular pressure tracings show that there is a pressure on the ventricular walls during diastole, equal to the diastolic pressure in the aorta. The ventricle is thus locally stimulated to increased exertion and its contraction becomes similar to that in which a muscle is extended before it contracts. So long as the heart is able to supply the increased demands thus made on its energy there may neither be hypertrophy nor dilatation, and we have the authority of Krehl[37] that every case of aortic insufficiency is not accompanied

35. Quot. by Gaskell, Shaefer's Text-book of Physiol.
36. Schaefer's Physiol., vol. ii, 170.
37. Clin. Path., trans. Hewlett, p. 38.

by an enlargement of the left ventricle. When, however, the cardiac muscle becomes inefficient it will give way to the stretching influences which bear on it during diastole, and the cavity of the ventricle will enlarge. This is immediately followed by hypertrophy. But in so doing the increased work which the heart now accomplishes, as a consequence of the greater systolic output, has the effect of raising the mean pressure in the arterial system. There is thus established a condition in which there is a greater transmission of pressure and a still greater expenditure of energy. The condition is a progressive one, for the greater the hypertrophy and dilatation the greater the transmission of pressure and consequently a greater waste of cardiac energy.

It is thus evident how potent a factor is a low peripheral resistance in the preservation of the heart in aortic insufficiency. It not only lessens the tendency toward the regurgitation of blood, but it also reduces

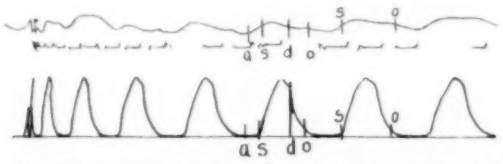

Fig. 36.—Simultaneous tracing from the left auricle and the left ventricle after the production of aortic insufficiency. a, auricular systole; s, ventricular systole; d, ventricular relaxation; o, opening of the mitral valves. There is a fall in the auricular pressure during the contraction of the ventricle. The valves must, therefore, be competent.

the influence of the increased tension on the ventricle as a stimulating agent.

It may not be out of place to mention here the frequency with which a transient mitral insufficiency may develop in the course of an experiment in which the aortic valves have been damaged.

A simultaneous tracing of the intraauricular and intraventricular pressures gives a ready means of detecting such incompetency of the mitral valves, for instead of the normal fall in pressure, which occurs in the auricle during ventricular systole, there is a systolic rise of pressure when an insufficiency develops. Such is seen to take place in tracings Nos. 36, 37 and 38. These three tracings were taken at different times during the course of one experiment.

In No. 36, there being a fall of pressure in the auricle during the contraction of the ventricle, s-d, the mitral valves are competent. In No. 37 there is a systolic rise of pressure, which is to be interpreted as indicating an inadequate closure of the auriculo-ventricular orifice.

Tracing No. 38 was taken an hour later, and it shows that the ventricle has recovered, for there is now a systolic fall in pressure in the auricles.

This effect is probably due to periodic changes in the ventricular tonus, which, when lowered, permits of ventricular dilatation, and this is followed by a relative insufficiency at the mitral opening. This view is supported by the result obtained by stimulating the peripheral end of the vagus, which produces a marked diminution in the ventricular tone.

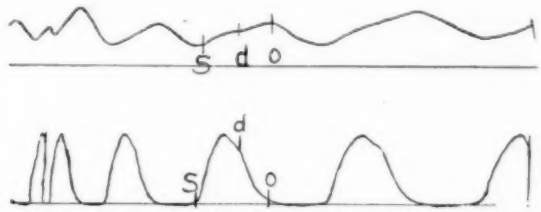

Fig. 37.—Same as No. 36, but there is a rise in auricular pressure during the contraction of the ventricle, s-d. The valves are incompetent.

Tracing No. 39 shows the effect of such stimulation. It will be seen that immediately before stimulation the ventricular systole, s-d, is accompanied by a slight fall in auricular pressure (the valves are competent), while during stimulation there is a marked rise in pressure (an insufficiency has developed). O marks the commencement of the fall of auricular pressure and, therefore, the time of opening of the mitral valves.

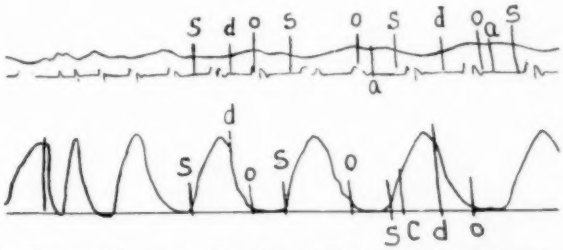

Fig. 38.—Same as No. 37, one hour later. The mitral insufficiency is no longer present, for now the pressure in the auricle falls during ventricular systole, s-d. Lettering as above.

It is clear that the production of a relative insufficiency at the mitral orifice, in addition to an aortic lesion, may, to a great extent, be avoided by lowering the diastolic blood pressure. For, when the diastolic pressure is sufficiently low, the ventricular tone is able to overcome it and no dilatation results.

The conclusion, then, which is to be drawn from the experimental and clinical study of this disease is that the condition which is most favorable in a patient suffering from aortic insufficiency is a low diastolic blood pressure. This is supported by the fact, long recognized by clinicians, that the outlook in a case of aortic insufficiency resulting from rheumatic endocarditis is more favorable than one in which the lesion has been the result of arteriosclerosis (Osler[38]). The reason is sufficiently obvious, for in the former the diastolic pressure is low, while in the latter, as a consequence of the rigid arteries, the diastolic blood pressure is high.

Finally, this is not without a bearing on the question of the use of digitalis in this disease. It has been contended that this drug is contraindicated because by prolonging ventricular diastole it favors increased

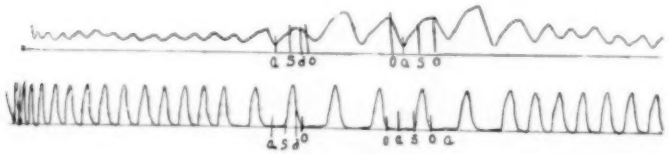

Fig. 39.—Simultaneous tracing from the left auricle and left ventricle after production of aortic insufficiency to show the effect of vagal stimulation. The diminution in tone causes a dilatation of the ventricle and a relative insufficiency at the mitral orifice. Before stimulation the pressure in the auricle falls during the ventricular systole, while during stimulation there is a rise of pressure from s-d.

regurgitation. But it has been proved already that a mere lengthening of the period of diastasis is not harmful, if there be no diminution of the ventricular tone, since the pressures in the ventricle and aorta are equalized as soon as the ventricular filling is completed. The harmful influence of digitalis can not result from its action in slowing the heart rate. It is due to the action which the drug possesses on the peripheral arterioles. As is well known, it has a powerful constricting action on these vessels, and thus, by raising the diastolic pressure, is its effect deleterious. Theoretically, strophanthus should be a more useful drug, since, as shown by Fraser,[39] it does not possess this constricting quality to the same degree.

38. Princ. and Pract. of Med., 1898, p. 517.

39. Action and Uses of Digitalis and Its Substitutes, with Special Reference to Strophanthus. Read before Brit. Med. Assoc., Cardiff, 1885, p. 15.

SUMMARY OF CHIEF CONCLUSIONS.

1. The work of Henderson is confirmed in that the cardiac cycle is not diphasic but triphasic, and consists of systole, the period of the ventricular discharge; diastole, the period of ventricular relaxation and filling; diastasis, the period of rest.

2. The effect of the production of aortic insufficiency in the dog is to increase the amount of systolic output by only a fraction of a cubic centimeter of blood.

3. The volume of blood which regurgitates is negligible.

4. The transmission of pressure to the ventricle increases the ventricular tonus.

5. It also produces a reflex inhibition of the vasomotor center.

6. The fall of pressure in aortic insufficiency is due to the diminished peripheral resistance thus induced, and is not caused by loss of blood from regurgitation.

7. The increase of pulse pressure—the difference between maximum and minimum pressure—is due to a lowering of the diastolic pressure. There is no increase in the systolic pressure.

8. The main fall in pressure is systolic in time and is due to an increased blood flow through the capillaries.

9. So long as the tonus of the ventricle is maintained, a slowing of the heart rate does not favor increased regurgitation.

Johns Hopkins Hospital.

THE DIAGNOSIS OF TYPHOID FEVER BY CULTURES FROM THE BLOOD OF THE EAR.*

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Although the diagnosis of typhoid fever by the cultivation of Eberth's bacillus from the patient's blood has now been practiced for some years, the methods hitherto generally employed have involved such complicated technic that they have been used to a very limited extent outside of hospitals. The cultural method of diagnosis, however, possesses two distinct advantages. In the first place, the blood culture is the method by which the earliest diagnosis can be made, inasmuch as the organisms appear to be present in the blood from the very beginning of the constitutional symptoms, thus usually a considerable time before the agglutination reaction is positive. Secondly, the blood culture is the most scientifically accurate method of diagnosis. At the Massachusetts General Hospital an agglutination reaction is considered to be positive if there is complete clumping and loss of motility of the organisms in a dilution of 1 to 50 in one hour. Any lesser reaction—where, for instance, some of the bacilli remain free and motile—is termed "incomplete" or "suggestive." Any one who has had considerable experience in the use of the agglutination test knows how often this "suggestive" reaction is met with. On the one hand, a case of typhoid fever may run for days, and even weeks, before a complete reaction is observed. On the other hand, owing to trouble with the culture, or to some, as yet unexplained, effect of the serum, diseases other than typhoid fever may give "suggestive," or even temporarily complete, agglutination tests. Thus a case of pneumonia—in a boy with no history of a previous typhoid infection—showed at the height of the course of the fever a complete reaction. Three days later, after the crisis, the temperature became normal, and the agglutination reaction was "suggestive." A week later it was absolutely negative. In fact, the more one observes "suggestive" reactions the less suggestive they become. It is natural, then, to seek a method of making an early and absolute diagnosis.

A great advance in blood-cultural methods was marked by the article of Conradi[1] in January, 1906, in which he described the use of a medium consisting of ox-gall, peptone and glycerin. With this medium he was able to demonstrate the presence of the etiologic organism in 50

*From the department of the Theory and Practice of Physic, Harvard Medical School.

1. Deutsche med. Wchnschr., 1906, xxxii, 58.

per cent. of 56 cases of typhoid and paratyphoid fever. The blood was taken from the ear by means of a pipette, was mixed with the ox-gall and incubated; from this mixture plates were planted on the following day.

In spite of these results, however, he believed that the best method was to take the blood from a vein. Conradi considered that most of the success of the method was due to the fact that bile prevents the coagulation of blood, and thus does away with the marked bactericidal properties of clotted blood.

Kayser,[2] who also reported cases in 1906, found that plain ox-gall gave as good results as Conradi's medium. By experimentation he showed that the inoculation of a tube of ox-gall with as few as 2-4 typhoid bacilli resulted, after incubation, in a profuse growth of the organisms. He is inclined to lay less stress rather on the fact that bile prevents the coagulation of blood than on the specific nature of the bile itself. When the frequency of gall-bladder infection in typhoid fever is considered, together with the numerous cases in which the organisms have been carried in the gall bladder for years after the acute infection, this latter view seems more plausible.

Kayser reports 200 cases. Five of the cases in the first week were paratyphoid fever, and in 4 of these the organism was obtained. All of 47 cases of typhoid fever in the first week gave positive blood cultures. In the second week 57 per cent. of 92 cases were positive. In the third and fourth weeks 40 per cent. of 56 were positive. Of the total 200 cases the etiologic organism was obtained in 65 per cent. Thirty-seven, or 18.5 per cent., gave the diagnosis by culture before it could be made by the agglutination test. Coleman and Buxton[3] obtained positive results by the use of Conradi's medium in all of 24 cases, in which the blood was taken between the fifth and twenty-first days of the disease. Veil[4] has lately reported 210 cases in which he used plain ox-bile as a medium. In the first week the cultures were positive in 78 per cent. of 32 cases; in the second week they were positive in 63 per cent. of 105 cases; in the third week in 43 per cent. of 44 cases, and in the fourth week in 22 per cent. of 20 cases. In the first week only 50 per cent. of his cases gave the agglutination reaction. In the later weeks the agglutination reaction was more constant than the culture.

The general method of these writers has been as follows: By means of a syringe 2.5 c.c. of blood are taken from a vein and added to 5 c.c.

2. Münch. med. Wchnschr., 1906, liii, 823 and 1953.
3. Am. Jour. Med. Sci., 1907, cxxxiii, 896.
4. Deutsche med. Wchnschr., 1907, xxxiii, 1450.

of sterile ox-gall in a test-tube. The mixture is incubated for about fifteen hours, when a few drops of it are planted on Endo's or Drigalski-Conradi plates. The colonies growing on these plates are then put through the regular cultural and agglutination tests for the typhoid bacillus.

In the following cases from the medical services at the Massachusetts General Hospital, an attempt has been made to put the ox-gall medium to practical use and to simplify the technic of blood cultures so that they may be used as a routine diagnostic measure in typhoid fever. The ordinary method of obtaining blood by inserting the needle of a syringe into one of the veins of the forearm is in itself a procedure too complicated for general use outside of hospitals. It involves thorough sterilization of the surface of the arm and of the operator's hands. It can not be done easily by one person without an assistant. To many patients the pain caused by the prick of the needle is decidedly disagreeable. Finally, there are not a few individuals with such small or obscure superficial veins that it is difficult, or even impossible, to get the point of the needle into them without a preliminary skin incision.

In all the following cases, therefore, the blood was taken from the patient's ear. Test tubes containing 5 c.c. of fresh ox-gall, sterilized in the autoclave, are used. The lobe of the ear is cleansed with alcohol and sterile gauze and then pricked with a small lancet-pointed knife. The blood is squeezed out, drop by drop, and allowed to run into the tube of bile. By careful manipulation 1 to 2 c.c. can be collected without any inconvenience to the patient. Not more than 2.5 c.c. blood should be added to 5 c.c. of ox-gall (Kayser), but up to this limit the more blood there is taken the greater the chance of obtaining the organism.

The test tube containing the bile and the blood is then put in the incubator for about fifteen hours. At the end of this time the medium shows no distinct gross change. Microscopic examination of a drop of the bile may show the presence of organisms, but, as they are sometimes difficult to see, a transfer of several loopfuls is made to a tube of coagulated blood serum. After from 3 to 5 hours of incubation, microscopic examination of the water of condensation shows the presence of motile bacilli. A transfer is then made from the blood serum to agar for a stock culture. Inasmuch as complete sterilization of the skin of the ear is often impossible, a contaminating growth of cocci may be present, but, since the typhoid bacilli grow much more rapidly than these, a transfer to agar from a young blood-serum culture will usually result in a pure stock culture.

The demonstration of a motile bacillus in the water of condensation

of the blood serum can be made in 18 or 19 hours at most, and this in itself appears very good evidence of a typhoid or paratyphoid infection. In no case was a motile bacillus found which proved on further investigation to be other than the etiologic organism. In order, however, to identify completely the organisms, they have all been shown to decolorize with Gram's stain, grown on glucose agar and litmus milk, and tested for agglutination with the serum of a rabbit immunized to the typhoid bacillus. The agglutination reaction is often difficult to obtain, for the freshly isolated organisms may be at first almost non-agglutinable. After growing them on artificial media for some time, and especially after making a series of cultures at intervals of from 24 to 48 hours, this resistance seems to disappear and the organisms are much more easily agglutinated.

The method here adopted has as its advantages, first, the use of blood from the ear, and, second, the use of coagulated blood-serum tubes instead of Endo's or Drigalski-Conradi plates. The need of special differential media is thus avoided, and, as the growth on blood serum is much more rapid than on agar plates, the results are obtained earlier. Moreover, experience has shown that if the organisms are not obtained from the blood-serum culture there is very little likelihood of obtaining them from the plates, even after a longer incubation of the bile. In fact, if the typhoid bacilli are present in the original culture, they are almost always present in large numbers.

Blood cultures were made from 33 cases in which the diagnosis of typhoid fever was made either by the agglutination reaction or by a positive culture. The following summary shows the cases by weeks and also the relation of positive cultures to positive agglutination reactions:

Stage.	Cases.	Agglutination. positive.		Culture. positive.	
		Cases.	Per Cent.	Cases.	Per Cent.
First week	5	3	60	5	100
Second week	19	14	73.6	15	78.9
Third and fourth weeks.	9	7	77.7	4	44.4
Total	33	24	72.7	24	72.7

It will be noted that these results compare favorably with the larger series of cases, in which the blood was drawn from veins. In 9 cases, or 27.2 per cent. of the total number, the positive culture preceded the agglutination reaction by from 3 to 7 days. In one of the cases an agglutination with the laboratory typhoid culture was never obtained, although the test was made at intervals throughout the course of the disease. The son of this patient, presumably infected with the same strain of organism,

gave a positive culture and agglutination test on entrance, but later in the disease the agglutination reaction became completely lost.

In one instance the typhoid bacillus was isolated on admission to the hospital, and again during the course of a relapse. Cultures taken during the afebrile period and at the beginning of the relapse were negative. In 4 cases the first culture was negative, while a second culture, taken a few days later, was positive, and in one case the first two cultures were negative, while a third was positive, giving the diagnosis before it was made by the agglutination reaction. It is thus advisable not to be content with one negative culture if the case continues to be suspicious.

The results of this and other series of cases go to show that in the early stages of typhoid fever the diagnosis can be made in the majority of cases by isolating the etiologic organism from the blood. Inasmuch as the requisite amount of blood can be so easily obtained from the patient's ear, there is no reason why the method should not be applied in every suspicious febrile case. The study of the culture and the identification of the organism is a comparatively simple bacteriologic process where laboratory facilities are available. In examining and reporting on cultures for practitioners who are not accustomed to doing their own bacteriologic work, a new field of usefulness is open to such public laboratories as already aid in making early and accurate diagnoses by performing agglutination reactions.

I am greatly indebted to the visiting physicians of the Massachusetts General Hospital for permission to use their patients; to Dr. J. H. Pratt for many valuable suggestions, and to Drs. J. H. Young and R. Kinnicutt, Jr., who have allowed me to include the results of bacteriologic examinations made by them.

THE BEARING OF METABOLISM STUDIES ON CLINICAL MEDICINE.*

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In a pursuit like the practice of medicine, in which we have two kinds of possible activities, one essentially very close to pure science, the other engrossing practical work, those engaged in these two fields are likely to draw somewhat apart. There is a strong tendency for many of those occupied with scientific matters to keep their minds so closely fixed on the abstract problems they are endeavoring to solve that they forget to reconnoiter as they go along, and to attempt to determine—and they often forget particularly to point out—what practical bearings they may discover by the way. A certain number of such workers, indeed, frown very readily on frequent excursions into the practical application of science, as being somewhat cheap and likely to mix science and empiricism. They forget that in practical medicine we make such a mixture constantly, and must do so. Our efforts must be to avoid hasty and unreasonable application of science, but to apply whatever we reasonably can, provided we thereby do no harm, even though it be not completely demonstrated that our reasons for the practical measures are absolutely sound, for it is but rarely that absolutely final proof can be given. The clinician, on the other hand, finds it exceedingly difficult to keep up a serious acquaintance with scientific medicine. Consequently, he often feels unable to get for himself the practical bearings of scientific work that is of a kind outside of his own immediate interests, and, hence, tends to neglect these bearings more or less entirely; or sometimes he goes to the other extreme and draws those unjustifiably broad practical conclusions from scientific work that especially offend his more scientific brother.

So far as there is any fault in this, it must be divided. It is, indeed, scarcely the fault of either, so much as of the present-day demands on both. Nevertheless it is not unfair for us to ask, with Oliver Wendell Holmes, that the medical scientist shall serve his knowledge "with special limitations and constant reference to practical ends;" but at the same time to demand that those of us who are clinicians remember that not only must scientific knowledge accumulate, but its principles even more than its details need to be comprehended, if practical medicine is to be

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benefited by it. In one of the wisest and most charming of recent medical books (Principia Therapeutica) Dr. Harrington Sainsbury says: "There are many who make light of general principles, knowledge of detail their sole demand; but this point of view sees one side only of the shield, be it silver or gold, as it shall please them; for while, doubtless, general principles without details make but a foolish business, it is no less true that details without guiding principles yield but a busy foolishness." My warm sanction of this remark and my feeling that both clinicians and medical scientists often make too indifferent a search for the practical guiding principles that may be derived from exact investigations were, indeed, the things that determined me to treat my subject in a general way rather than by going into a detailed discussion of specific facts of the subject. Studies of metabolism, in the broader sense of this term, are, I think, a more fruitful source of clinical principles than is any other form of investigation, unless it be that relating to hygiene. The most direct reason for this is that they are carried out on living beings and deal with living processes while the latter are still in action. A more prosaic but still not inconsiderable further reason is that a large part of the conclusions are derived from actual figures, often, indeed, by balancing one column of figures against another. Figures are very convincing and clarifying to the human mind, and give much less opportunity to indulge any unconscious personal bias than does clinical observation, or even morphologic or most other accurate studies into which figures do not enter, and it is in ridding him of bias that investigation is most useful to the clinician.

SCIENTIFIC AND LITERARY STYLE.

In his essay on "Style" Walter Pater describes the scientific style as presenting facts painstakingly as such, unembellished by imagination, while the literary style, "as it more closely approaches fine art," becomes more and more the presentation of facts, not simply as such and as accurate truths, but in the form of truths as they appear to the writer —"soul facts," as he calls them. Considering that he is working for the art of medicine as well as the science, I think the medical scientist often presents his facts too little embellished, but, on the other hand, being a clinician, I may say without impertinence that, surrounded as he is by impressive human happenings and a complexity of the details of disease, the clinician's tendency—a tendency that it is always his earnest desire to avoid—is frequently to make for himself "soul facts" that do not bear contrast with the real thing, if the latter can be found. Nothing, to my mind, succeeds better than a few figures in determining whether

our conceptions are scientific or "fine art." These figures sometimes destroy idols and may leave nothing in place of them, but this is, at least, more satisfying than error. They often simply confirm vague beliefs or traditions that were based previously merely on observation, but this gives confidence in place of uncertainty. Frequently they yield new facts that could have been learned in no other manner.

Among the many ways in which metabolism studies have already influenced clinical medicine and will continue to do so, I have been particularly impressed with some of those that often escape notice, chiefly, I imagine, because they are so simple and elementary that serious students of the question scarcely think any more of many of them. Among the most prominent of these, to my mind, is the effect that such studies have quietly exerted on the clinical use of changes in excretion in reaching diagnostic and therapeutic conclusions. In this point more than in any other, perhaps, there has been the tendency among clinicians to use details irrespective of the principles that govern these details. Some of the simplest principles of metabolism have often been overlooked, and, as a consequence, false diagnostic premises have often been built up. A correct appreciation of our knowledge of metabolism has served chiefly an iconoclastic end in this connection, but it is none the less serviceable; for no thinking person can doubt that to destroy a false belief is quite as useful as to demonstrate a new truth.

RELATION OF EXCRETION TO INGESTION.

The older literature was burdened with discussions of the value of things so inevitably unreliable as the determination of the percentage of urea, of uric acid, of various other excretory products, and of sugar, in a specimen of urine, without any consideration of the relation of this specimen to the total amount passed in the day. Such measures are, indeed, still carried out to some extent, as indications of the excretory capacity of the kidneys, of the kind and extent of any metabolic disorder that may be suspected, or as an indication of the severity of a glycosuria. It does not take a lively imagination to realize that variations must occur in accordance with the period of the day at which the specimen has been secured, but it has been necessary to accumulate demonstrative evidence of this to convince many minds; and some persons even yet remain so unfamiliar with the basic facts of excretion that they still fail to comprehend so simple a principle, and do not realize that first of all the mixed urine of a twenty-four hours' period must be studied if one is to have the slightest idea even of the real amount of any substance that is being excreted.

So simple a fact as this is readily understood and comparatively little neglected now by careful clinicians; but, though it would seem to be equally true without demonstration, it takes much more emphatic evidence to convince most persons that the excretion of any substance varies with the amount taken in of the substance itself, or of the foods that yield it. It is fruitless to attempt to reach any accurate conclusions on the basis of studies of excretion unless one knows the amount taken in of those substances that influence this excretion. There is a general comprehension of the fact that a glycosuria is largely influenced by the diet; the relation is, indeed, so direct that it is traditional lay knowledge. But this knowledge is even yet too infrequently considered in judging of the severity of a glycosuria, and it has taken a long time to convince many who have little interest in metabolism that estimations of urea mean nothing unless accurately contrasted with the amount being taken of urea-yielding foods. If those who in their studies of renal cases have made urea estimations—and especially our colleagues, the obstetricians, who have devoted much discussion to this method of diagnosis—had had the opportunity to see the nitrogen excretion in a normal person vary from a few grams to thirty or more, in accordance with mere changes in diet, the time that they have lost over this point would have been saved. Accurate metabolism studies carried out chiefly by von Noorden and his students have, indeed, shown us how impossible it is, even in marked nephritis, to reach any certain diagnostic or prognostic conclusions from the most careful attempts to demonstrate retention, for retention is by no means the rule even in very bad cases, and it ordinarily varies with excessive excretion; and where retention occurs it may be due to poor excretion or to actual building up of tissue, the latter, of course, being usually a good omen rather than a bad one. A number of other factors, such as the absorption and excretion of edema fluid, also influence results so largely that clinical deductions are usually unwarranted from such studies.

THE VALUE OF CRYOSCOPY.

This same point of view that I have just been discussing might have saved medical and surgical clinicians much useless labor in more recent years in other studies of the functional capacity of the kidneys. A very large part, for instance, of the work that has been done regarding the excretion of sodium chlorid in renal disease has been carried out without any consideration of the diet, and all that work is, therefore, nearly or quite worthless. In most of the work on cryoscopy also the diet has been neglected, and the results are, therefore, especially in cryoscopy of the

urine, almost entirely valueless. Indeed, because things are excreted in different form from that in which they were ingested, we have no way of telling accurately what effect changes in diet would have on cryoscopy of the blood even, and especially on cryoscopy of the urine, except that we can test the influence of an absolutely exact standard diet in numerous different individuals, and can take an average of this and call it a normal. While the results would perhaps be reasonably accurate in normal persons, changes in metabolism as well as in excretion would largely affect the result, and we have no means in any cases under observation of telling whether the abnormalities are the consequence of metabolic or of excretory conditions. Therefore, a method that is in itself so exact as to fascinate the mind becomes clinically of little value in studying disorders of excretion, except in contrasting the concentration of the urine as secured separately from the two kidneys. Neglect of this view of the question has, it appears to me, led to a great deal of time being wasted in attempts to use this method for the elucidation of questions that it could not clear up.

Similar remarks apply to various similar studies and conclusions. Theories, and even descriptions of distinct diseases, have, for example, been built up on the mere presence of precipitates of oxalates and phosphates in the urine. There are some interesting questions, as yet not solved, regarding the relation of oxalates to digestive disturbance; and, to my mind, there is a much broader and more interesting relation than is usually admitted nowadays between so-called oxaluria and metabolic disturbance.

I have seen some exceedingly curious examples of a close relationship between oxalate precipitates and clinical symptoms; such, for instance, as a mania of a few days' duration in the convalescence from an acute pneumonia, the urine containing oxalate crystals during the period of mental disturbance, but not before or after. The oxalate precipitates, I take it, are merely an index that something else is going wrong; they are, of course, almost certainly not the evidence of oxalic-acid poisoning, and usually not evidence that the amount of oxalic acid in the urine is increased.

As to the phosphates, theorists have even gone so far as to describe distinct nervous disorders due to a loss of phosphates from the system, basing this almost solely on the presence of precipitates of phosphates in the urine. Real studies of metabolism have, of course, in most such cases, shown that there is no excess in the urine; that the phosphates precipitate because of conditions unfavorable to their solution, or if the amount

happens to be large it is ordinarily because an excess has been taken in the diet. There are unquestionably peculiar and interesting problems to be worked out in connection with some of these cases of phosphate precipitates. In some instances they present almost a definite syndrome, particularly certain cases in which I have been much interested in which the urine periodically becomes alkaline, phosphates precipitate out, and this is soon followed by a migrainous headache, and subsequently by symptoms appearing to indicate that the individual is eliminating toxic material through vomiting, diarrhea or diuresis. The attack is then over. In some cases with phosphate precipitates I have found the rather curious condition of an excessive excretion of ammonia, without any apparent reason for it. Ordinarily excess in ammonia excretion means, of course, the presence of an undue amount of acid in the system, and the excess of ammonia is present in the urine simply because it has been used to neutralize the acids, but in these cases there is no evidence of acidosis. The conditions, indeed, are so far from it that the urine is alkaline when passed. What such conditions mean I do not know.

A similar instance of a hasty conclusion that was soon set right by real investigations of metabolism is the claim made a few years ago by some of the French school that pulmonary tuberculosis is associated with and more or less dependent on a "demineralization" of the tissues; that there is a regular loss of mineral salts from the tissues. This statement was soon corrected by accurate metabolism studies by Ott and others, and it need never have been made had a proper contrast of intake and outgo been worked out in the beginning.

THE "URIC ACID DIATHESIS."

In no relation in the whole range of medicine has this point of view been so thoroughly obscured and so often lost sight of as in all the labor that has been expended on the building of idols of uric acid and in breaking these same idols afterward. A very large part of this labor might have been saved could both clinicians and physiologists have started with the same conception that we have long had regarding other excretory products, that is, that the excretion is largely influenced by the amount of uric-acid-yielding foods taken.

Whatever direct relation to the causation of disease uric acid may ultimately be shown to have—and this, I think, will probably be slight—we have, at least, learned that mere studies of its excretion are of little, if any, clinical value; first of all, because the amount excreted is, in large part, directly dependent on the kind of food taken, and, worse than this for the clinician, because a certain amount is formed in the organism

and not only directly from tissue breakdown, but also, almost certainly, synthetically. We do not know how much this is normally, and can not tell at all, therefore, how much it may be in disease. To add to the complexity of the question, we have learned that some of that derived from the food, and some that is formed in the organism, is altered to other substances in its travels through the body, but we do not yet know how much, and we know almost nothing about the way in which some of these variable factors are influenced by most diseases.

We can not, therefore, by the most exact methods of studying excretion tell more about uric acid or the total purin metabolism than that the amount of the various purins in the urine is larger or smaller than it should be on the diet then being used; and that this may be due to abnormalities of excretion or to disorders of oxidation, synthesis or other metabolic processes. We have no accurate scientific conception as to which is at fault in any particular instance.

When I was graduated in medicine, stress was still often laid on uric-acid precipitates as indicative of disease depending on uric acid. Yet it was apparent, even long before this time, that such precipitates mean of themselves nothing regarding the amount of uric acid in the urine, but are due to the effects of low temperature or chemical changes in the other components of the urine that affect the solubility of the uric acid. Traces of such elementary error in teaching, however, still remain in some medical writings that carry authority. When we learned laboriously the striking influence of diet on uric-acid excretion, the door appeared to be open to some definite knowledge; but the relative effects of abnormalities of synthesis, oxidation and excretion can not yet be reckoned with at all.

So far as I can see, of all the clinical uric-acid idols, at least of all those relating to the excretion of uric acid, but one remains—the recently determined fact that gouty persons excrete but a small amount of endogenous uric acid, and they excrete the uric acid derived from the food slowly or imperfectly, if one makes careful quantitative studies of the excretion over a period of many days. This idol, too, I strongly suspect, will in large part fall. The diagnostic, and to some extent at least the therapeutic, conclusions built on it will, in that case, fall with it. I have already observed cases other than gout in which the same thing occurs strikingly, and other persons have done the same. Probably this will prove to be frequently true, and the abnormality will be shown to be the result of so many causes that it can have no important significance in relation to gout from the diagnostic standpoint. Yet, though the status of the studies of the excretion of uric acid is what I have indicated, I am still frequently met with the request, from some of my most respected clinical associates,

to point out to them how they can get help in their diagnoses by making studies of the amount of uric acid in the urine. It may be that better results will be obtained from studies of the exact amount in the blood, a method that has recently been systematically used for diagnostic purposes, but the value of such studies is not yet clear, for many of the above mentioned objections apply to it also and it is too difficult for ordinary clinical purposes.

Such are examples of "soul facts" that have been demonstrated to be such through metabolism studies, and as a consequence of our better knowledge, the false diagnostic and therapeutic conclusions built on them have more or less completely disappeared. The influence of metabolism studies, however, has been by no means solely iconoclastic. Probably in no line of medical work have the methods followed been more purely empirical until recent years than those used in dietetics, and yet in scarcely another line of work has so much labor been expended in the last generation in accumulating facts. These facts are, however, only beginning to be widely appreciated. Dietetics is much less a matter of mere experience and personal opinion than it was. All humanity finds it much more difficult to make use of new knowledge and laws relating to the things that we have grown up with than in connection with matters that are themselves new and strange, and food is so old a story that it is difficult to teach ourselves to examine into its use in medical practice in much the same way that we study the use of other therapeutic measures.

DIETETICS.

In dietetics we remain more prone than in most other medical practices to work with details, regardless of principles, instead of using whatever principles we have in leading us to correct details. Indeed, it appears to me that a writer to whose wisdom I have already emphatically referred comes very close himself to recommending in dietetics the "busy foolishness" that he so scorns in drug therapy, when he practically advises us not to bother our heads about the discussions of food standards, but to attend to the details that suit the individual.

We must always arrange our diet for individuals, and not for a mere average human being. But in dealing with serious conditions by using drugs we are dependent, first, on knowledge of what the action of a drug really is, and, in the second place, on knowledge of the dose that is usually effectual and safe. If we would be accurate in regard to the much more vital question of foods—and particularly if we would be accurate in dangerous cases, in which we ourselves are largely responsible for the amount and character of the diet and in which, if any grave errors

occur, we alone are at fault—we must know, first of all, what the actual nutrient powers of the food we use are, and how much of it an average individual ought to have, if he is to be neither starved nor overburdened. It is quite true that the physiologist asks a little too much of us when he presents the matter to us, as he often does, in such a form that it would appear that to arrange a diet with reasonable accuracy is almost the same thing as to conduct a laborious physiologic experiment, and both the physiologist and the clinician discuss these standards too much as if they were absolute things, that are meant to be followed literally, instead of being simple guides; and yet at the same time that he demands absolute rules the clinician sees the impossibility of constant standards, for he knows that we deal with complexities of disease and temperament that make absolute accuracy a thing that even the physiologist can not reach with his most exact methods, and that with patients who are not seriously ill it is utterly impossible in ordinary practice to be more than approximately accurate in attempting to make dietary regulations approach standards. Hence he often objects that these standards are worthless and makes no attempt to use them. But the clinician might remember that he does not demand absolute standards in other things, as, for instance, in the use of drugs. He makes allowance for temperament and for peculiarities of disease in such things, but in this present day he would be looked on as a dangerous character if he had not learned what the pharmacologist has taught us as to the effect of drugs and the amount that may wisely be used with the average individual.

If it were a general custom to look at foods, first of all, from the same point of view as drugs are looked at—from a consideration of the kind and amount of their food value, on the one hand, and of the food demand of the average individual of a given size, on the other—we should less frequently see persons fed on a diet that may be big in bulk, to be sure, and that may look impressive on the records; but that is composed of material of so little food value that the whole amount evidently means a considerable degree of starvation when its caloric value is contrasted with the real demand. We should then less frequently see disease made more grave and convalescence more prolonged through the use of such a diet, and we should have been quicker to recognize, for example, that profound exhaustion, fever, delirium and other symptoms in the later stages of acute disease and in the convalescence—particularly in typhoid fever—are the result of too limited a diet quite as frequently as they are due to continued toxemia, a fact that is particularly true in dealing with children. On the other hand, we should see less enthusiasm over many of the so-called "free diets" used in typhoid fever during recent years if

we were accustomed to looking at a diet list in such a way that it becomes apparent that many of these free diets are, to be sure, more solid, but at the same time less nutritious, than is a reasonably generous milk diet.

Such methods can easily be used in severe disease, for, with a patient at rest, his food demand is apparent, and the diet is simple and its value easily determined. A little practice gets one into the habit of thinking in this way. When diets are more complex, we must trust chiefly to judgment, to the patient's appetite, and to observation of the effects, rather than to figures, in regulating the amount of food, but even here we can avoid such gross errors as burdening a delicate child with an amount of food that possesses two and a half times the amount of calories that an adult would need and wondering why his health does not improve—an example of what I have seen done. If, too, we followed some of the details of clinical studies of metabolism and absorption we should know, for instance, that over-generous feeding in conditions like pulmonary tuberculosis is not only evidently likely to tax digestion, metabolism and excretion; it has also been shown often to result merely in burdening the digestive tract and in expulsion of much of the food, especially much of the fat, in the feces; so that the end-result is merely to overwork digestion and to waste food.

I can state without fear of contradiction that the number of clinicians that habitually use the available knowledge of dietary standards, food values, digestion and absorption of foods, the behavior of foods in the course of metabolism, and the chief excretory products of food, in helping them to plan their diets, is extremely small as compared with the number that employ whatever accurate knowledge we have in connection with the much less serious question of the use of drugs. I believe that quite as many patients are damaged by faulty use of foods as by faulty orders concerning drugs. Our knowledge of these various questions concerning dietetics is very imperfect in many particulars, but it is no more imperfect than is our knowledge of drugs and many other therapeutic measures.

SPECIFIC DIETS.

There are, it appears to me, two striking errors besides inexactness in the general view of dietetics—errors that our knowledge of metabolism can largely set straight at once. One is that often vague, but nevertheless common, feeling that the details of a diet should be specifically suited to the disease in which it is to be used. We have got well past the point where we thought drugs to be frequently specific in their action. We should make the same confession in regard to diet, and we should get

farther. We know almost nothing about any actually specific alterations of general nutrition that may occur in specific disease, and we know comparatively little of the specific effects of different foodstuffs on normal nutrition.

To attempt to arrange actually specific diets is, therefore, in most diseases impossible; and it is questionable whether we shall ever get to the point at which we can do this. Just as in the general treatment of particular diseases our measures are almost always directed not against the disease as such, but against certain conditions that occur in that disease (these conditions, however, usually occurring in many other diseases, in different combinations), so, in diet, do we study and treat, not diseases, but conditions, such as overnutrition, undernutrition, irritability and sluggishness of the digestive tract, exalted and sluggish metabolism and difficulties in excretion. Dietary studies have taught us how to meet with considerable exactness general excessive or reduced nutrition, in most instances; and also how to prevent such conditions. Such studies have also given us much knowledge of the suitability of most foods in controlling or preventing the general types of digestive disturbance that I have mentioned, and they have taught us an appreciable amount concerning the reduction of the labors of metabolism and excretion through proper choice of foods. We have much yet to learn, but we do not make use of what we have learned. If we can start from the standpoint of learning the general type of the condition that we are dieting, and can then apply the general principles of our knowledge of metabolism and of foods to this, the question of details will afterward become comparatively easy and will be simply dependent on the gradual elaboration of one's skill in details.

The next most impressive dietetic error, it seems to me, is to restrict narrowly or largely exclude most or all the members of a class of foods, because there seems to be an especial difficulty with this class. We commonly encounter the order, for instance, to "stop using starchy foods"; and often, as a result, carbohydrate foods are more or less completely excluded from the diet. Unquestionably, we have been clearly taught that a considerable amount of protein is essential, and in recent years we have equally well learned that an even larger amount of carbohydrate is almost as necessary for the proper performance of the chemistry of the body processes and especially in avoiding acid intoxication. A reasonable amount of fat is also at least extremely desirable, because of its great food value. These facts sufficiently indicate that our efforts should not be directed toward the exclusion of the whole of a peccant class of foods, in case some of the class disagree. We should, on the contrary, develop

sufficient knowledge of food composition and food preparation to be able to choose from the troublesome class varieties that will themselves agree. This we can usually do. It should be our chief effort to keep the amount of each class approximately near the normal, except when temporary complete rest from some one class appears to be needed, as occasionally happens. If wide variations from the normal are very harmful, it is probably true that even moderate variations from the normal are at least disadvantageous, especially if persisted in.

Such are some of the main principles that we can derive from dietary studies, but there are many other points that could be discussed. For instance, simple intake and outgo experiments have shown that it is exceedingly difficult to make a normal person gain in protein tissue by feeding, but they have demonstrated how greedily the convalescent retains protein. He is in much the same state as is the growing child in this regard. A proper appreciation of such a point as this makes one realize much more clearly that by taking advantage of this tendency and wisely pushing matters in convalescence we can not infrequently transform a disease from a curse into a blessing by keeping metabolism on the run, so to speak, thus making tissue growth go farther than the previous amount, and changing a person previously ill nourished into one whose nutrition is comparatively good. The same principle holds with the infant. Not only does the infant or child retain large amounts of protein; this very fact, as well as simple reflection, indicates that large amounts are needed at this period of life, and I firmly believe that in recent years the minds of pediatrists have been so fixed on the digestive tract and on the dangers of high protein feeding that general nutritional demands have been half forgotten and many infants have been injured by giving them too little protein.

There are numerous other ways in which a knowledge of metabolism, even though it can not be so directly translated into action, is nevertheless indirectly influential in determining a broad and comprehensive action instead of a narrow and mistaken one. One of the simplest instances of this, for example, is diabetes. We are much better off clinically to know that there is no evidence, except in the late and grave stages, of a toxic tissue destruction in diabetes; that treatment directed to the elimination of a toxemia would be superfluous, and that the anomaly, whatever its actual nature may be, appears in ordinary instances to produce a tissue loss simply because there is a food loss due to the glycosuria, and the glycosuria largely explains all the other typical symptoms, even the acidosis and the coma that may occur. This makes much more clear the entire dependence of successful treatment on diet.

The severity of the disturbance in various diseases has often been made clearer by balancing figures against each other. One of the most striking instances of this that I have ever seen is a case of simple purpura that I have recently studied, one of the type that affords no clinical evidence of constitutional disturbance and hence is said to have no constitutional symptoms. This patient, when studied metabolically, showed a high grade of tissue loss with each outbreak of purpura, demonstrating clearly that he had severe metabolic disturbance and that some metabolic disorder in all probability produces his attacks; for the amount of hemorrhage was not sufficient to have been of itself responsible for the disturbance of metabolism.

The effect of different forms of treatment can frequently be made much more apparent by studies of this sort. For instance, I have recently investigated a case of direct transfusion by Crile's method, in which the clinical results and the effect on the blood indicated solely improvement in the patient's general condition and his blood count. A metabolism study, however, showed very striking tissue destruction, with some features that indicated that it was almost certainly not due merely to a breaking down of the transfused blood, thus showing that the effects of this operation may at times, in diseased persons at least, be much more extensive than merely to provide more blood for the patient, and it would seem that these effects may occasionally be very dangerous, for when a second transfusion was done in the same patient death speedily followed. Similarly, I have acquired a much more serious respect for the effects of the *x*-ray from having observed the remarkable influence that it can exert on metabolism, and having seen how easy it may be for the *x*-ray to cause tremendously good or dangerously bad results in ways that are not readily made apparent through ordinary clinical observation or through other methods of study.

The results of simple intake and outgo estimations often, too, make more apparent the nature of conditions, and especially whether there are or are not evidences of toxic tissue destruction, and, therefore, whether we can wisely use eliminative measures, or whether these would probably be positively harmful because not indicated. These are instances of the numerous ways in which metabolism studies of the simplest form—namely, balancing intake against outgo—have influenced our clinical conceptions of disease and of the manner in which various kinds of disease should be managed. There is, however, a vastly broader aspect of metabolism investigations.

Beyond all other things it has always been apparent, and in recent years more and more evident, that in order to gain an intimate acquaint-

ance with metabolic processes in normal or diseased persons we must not limit our studies to a comparison of the intake and outgo, and to a determination of the grosser changes in the excretions, the body fluids and the tissues, but must acquire a closer knowledge of the intermediate changes that occur in the course of digestion and in the synthesis and breaking down of tissue, and must learn the kinds of things that favor or interfere with these processes. Many tentative efforts were made to do this, but the tangible knowledge that they provided was slight, because the work was done somewhat blindly, until within the past few years, when two remarkable changes have occurred in our point of view and have opened the threshold to a new era in studies of metabolism.

TISSUE FERMENTS.

One of these is the conception we now have of the activity of ferments in tissue processes, a conception originally due to Salkowski's initiative; the other, the conception that we now have regarding the constitution of the protein complex, the meaning of the changes in protein that occur in digestion and metabolism, and their bearing on the breakdown and synthesis of tissues—a conception that was in the beginning due largely to the work of Kossel and his school, and in more recent years has been elaborated to a marvelous degree by the work of Emil Fischer and numerous others that have worked with him.

It is a striking fact that in the last-issued edition of Neumeister's *Physiologische Chemie* its then prominent author should have felt justified in stating that the observations of Salkowski and others concerning the presence of ferments in the tissues meant merely that these ferments were absorbed from the digestive tract in zymogen form, not that their production had any relation to the essential activities of the tissue cells, and that this statement should have been followed very soon after by the address of Hofmeister in which he predicted that it would be shown that most tissue processes, synthetic or catabolic, are largely dependent on the activities of ferments produced in the tissues. A few years ago we looked on ferment processes as confined to the digestive tract. Now the very name "digestive tract," so far as it applies distinctively to the kind of processes that go on in the stomach and intestines, has become almost a misnomer, for it has been made apparent that the same general kind of processes go on in the tissues everywhere, products similar to those produced in the alimentary tract being formed by ferments similar to the so-called digestive ferments. The distinction between digestive and tissue processes, even synthetic tissue processes, has grown still more indefinite since we have learned the influence of ferments on synthetic processes,

and especially since it has been actually demonstrated through the work of Croft Hill, Kastle and Loewenhardt and Alonzo Taylor that individual carbohydrate, fat and protein ferments do really have the function of building up, as well as of breaking down—that the same ferment does either of these two apparently opposite things, the result being dependent on the conditions in which it acts, and not on the nature of the ferment itself.

The profound emphasis thus laid on the importance of study of the conditions in which ferments act directs attention particularly to the exaggerated optimism that has somewhat generally, among clinicians, been centered on securing and using therapeutically ferments that are active in tissue processes. Even scientific workers have held forth alluring prospects in this connection. As a matter of fact, we can not manufacture substances that are so dependent on life processes for their existence as are tissue ferments—that often, indeed, are probably dependent on the unchanged structure of living protoplasm. We can not be sure that we shall ever be able to separate most of them in satisfactory form; and when we get them, as we do now, they are usually damaged and made more or less ineffective, often destroyed, by the processes through which they are put; and even if we secure them in satisfactory condition we have not yet obtained the slightest reliable evidence that we can, to any noteworthy degree, influence tissue processes by their therapeutic use. We even have no satisfactory evidence that their use influences digestive processes in the alimentary tract to any noteworthy degree. We have, therefore, it appears to me, excellent reasons for being very guarded about basing any serious hopes on the use of ferments themselves, in attempting to influence the processes in which they are normally active.

On the other hand, what a wealth of reasonable suggestions for interesting future work is given by the fact that it is not the ferment itself, but the medium in which it acts, that determines so profoundly important a result as whether the effect is to be construction or destruction; and what alluring possibilities in the distant future are offered by this as to the possible control of nutritive processes and of disease. It is highly probable that it is merely a change in medium that causes previously existing ferments, which have been inactive, to become suddenly active after a pneumonic crisis, and to digest the exudate with astonishing rapidity. The same thing is probably true regarding the involution of the uterus that begins with the beginning of the puerperal state. Indeed, it appears to me not improbable (though entirely unproved) that in this instance the change occurs directly from constructive action to destruc-

tive, for the growth of the uterus in pregnancy is a growth, not so much, if at all, in the number of the cells, but merely in the amount of tissue in the cells. It is quite possible that in pregnancy there is a ferment-constructive process, and that in the puerperium destructive work is done by the same ferment or ferments.

Such things are at the present time matters largely of speculation. I speak of them only in that sense and mention them merely as illustrations of what such studies may ultimately lead us to in regard to our powers of controlling normal nutritive processes and disease. We already know great numbers of things that influence ferment processes, and it is not improbable that we even now have in our armamentarium things that have much greater powers in this regard than we at all appreciate, and that we may gradually learn to make proper use of these powers, if we proceed from the correct point of view, and not merely from blind empiricism.

One way in which it appears to me to be probable, though as yet undemonstrated, that we actually do control, to some extent, the medium in which the ferment action takes place, is in the management of some of those cases in which acid intoxication occurs. The acidosis of diabetes appears to be largely dependent on the diet and on the inability of the organism to make use of carbohydrates, and it is possible that it is entirely dependent on these things, but there are numerous instances in which diet seems to be a factor of very little, if any, consequence in producing the acid intoxication that occurs as a part of the disorder—cases such as phosphorus poisoning and acute yellow atrophy, uremia, the recurrent vomiting of childhood, postanesthesia acidosis, grave anemias, and probably the pernicious vomiting of pregnancy. A number of these disorders seem, from accumulating knowledge, to be associated with tissue lesions and with alterations in metabolism that indicate that there is an abnormal activity of the proteolytic tissue ferments, particularly in the liver, and that this autolysis probably produces the acid intoxication secondarily. The acid intoxication in all probability then, in its turn, increases the autolysis, for Hedin and Rowland and others have shown that a slight acidity favors autolysis. Thus it is probable that a vicious circle is formed, and the effects increase from their own momentum. This conception is practically an application of the knowledge regarding autocatalysis to pathology. Clinically, in some of these cases, direct treatment of the acid intoxication with alkalies does good, but their action is most uncertain and unreliable. In bringing forward the evidence that acid intoxication is seen in the recurrent vomiting of children, I reported cases in which alkalies unquestionably did great good, and I have ob-

served some such cases since; but the result is highly uncertain and can not be anticipated. It appears to me somewhat probable that what we actually do in some of these cases by means of alkalies is to control whatever evil effects there may be as a direct result of the acid intoxication and, what is much more important than this, to provide a less favorable medium for the autolytic ferments to act in. If this is true, it is probable that the results are uncertain largely because the destructive changes that have already resulted from autolysis are so variable in their degree. If they have not been severe, the symptoms, no matter how severe they may be, will be controlled by stopping the progress of the ferment action; but if severe lesions have already occurred, no matter how mild the symptoms may be, control of the primary condition will not control its already grave destructive effects.

I have suggested another direction, also, in which it is possible that our study of the means of accelerating or retarding ferment action may have interesting clinical bearings. I have expressed the view that the *x*-ray exerts its action on the deeper-lying tissues, in part, at least, through influencing ferment action. This is by no means definitely proved, but there is some creditable evidence in favor of it. Starting with this conception, I have studied the effects of the *x*-ray in a condition in which our knowledge indicates that the desirable but hitherto often unattainable therapeutic measure is to accelerate or excite ferment action; namely, in unresolved pneumonia. Unquestionably the *x*-ray has had a very remarkable effect on metabolism in cases of this kind that Dr. Pemberton and I have studied, and there has apparently been a very strikingly good effect clinically on the consolidation in the cases that I have so far observed. My conclusions may be wrong in these instances, but I think that these are examples of the interest and the possible profit pertaining to systematic attempts to work out practical methods of influencing tissue ferments.

Similar studies will not improbably help us to understand the manner of action of things that we have already used without comprehending the way in which they accomplish their unquestionable effects. Unpublished observations that Dr. Caspar Miller and I have made indicate that the remarkable effects of mercury in acute poisoning, and probably in syphilis, are, partly at any rate, due to its causing increased autolysis; a suggestion that Dr. Flexner made publicly while we were working on this matter. Also some studies that I have not as yet completed, suggest that one way in which sunlight produces its pronounced effects on nutrition is through its influence on the same kinds of processes.

STUDY OF PROTEIN-COMPLEX.

Closely interlaced with the investigation of the tissue ferments is the study of the protein-complex and the products that it yields on digestion. Biologic observations have made it apparent that there are differences in the proteins of various species that simple analytic chemical methods do not show. The studies of recent years have probably demonstrated what the most important chemical differences are. Proteins of different species may or may not differ in the amounts of nitrogen, hydrogen, oxygen, sulphur, phosphorus and other elements that they contain, but this is not the essential question. A Norman and a Gothic cathedral may contain the same amount or different amounts of stone, mortar and glass. The essential characteristics of the architecture of such structures are not determined by the total bulk of the primary substances of which they are made, but by the manner in which the stone and mortar and glass are first put together to make columns, windows and other parts of different forms, and by the manner in which these are then employed in completing the whole. So in various proteins are the chemical elements first put together to form simple structures, the various amino acids, and these are then joined together in various amounts and to some extent in various kinds to form the different varieties of protein. Digestion consists in the fragmentation of the complex structures into the simpler structures. These latter are then put together in different amounts, and, to some extent, different kinds, to reconstruct the variety of protein desired.

This entirely alters our conception of digestion. Previously we thought of it practically as merely the hydrolysis of protein into forms that are dialyzable, and the purpose appeared to be simply to get protein into such a state that it could pass animal membranes and get into the circulation. The serious subject of discussion was chiefly where and how the building-back into native protein occurs, for albumoses and peptones could apparently not enter the circulation, since they have toxic effects. Our present conception of the chief purpose of digestion is that it breaks down foreign protein into the parts that make up the whole, in order that these parts may then be used in suitable amounts in reconstructing protein of the structure proper in the individual that is to be nourished.

It is highly probable that in abnormalities of this process of fragmentation and reconstruction we shall find the causes of some nutritional disturbances. We are all familiar with instances of digestive disorder associated with more or less profound nutritional disturbance, and we know that the disorder of nutrition may be vastly more severe than the apparent disorder of digestion. I have recently described cases of infan-

tile atrophy and other obscure forms of emaciation in which the proteolytic ferment powers of the intestine were greatly reduced—whether as the result of actual absence of proteolytic ferment, or because other conditions of the contents of the intestinal wall in these cases were unsuitable for ferment action, I do not know. In other forms of extreme emaciation of known causation, the ferment activities were normal. I have since investigated further cases that have given the same results. These observations lend some support to the hypothesis that I have suggested, that disorder in the fragmentation of the protein food or in the reconstruction into circulatory or tissue protein, or in both these processes, may prove to be the chief explanation of the nature of such conditions.

In matters such as these we are wandering in regions that are as yet too little explored for us to be able to come to very definite conclusions as to the meaning of results that have already been obtained, and we can not yet ask that the practical application of this knowledge in diagnosis and treatment should be at all clear. We have a glimpse, however, of the possibilities of productive work that will bear directly on our conception of normal and disease processes, and that will probably in time greatly enlarge our powers of recognizing the nature of disorders and will ultimately lead to enlarging our powers of controlling them.

Our knowledge of the activities of ferments in the tissues and our present conceptions of the protein-complex and its changes in digestion have already entirely altered our conceptions of the nature of many normal tissue processes and of numerous diseases. The manner in which the most striking lesions are produced in phosphorus poisoning and acute yellow atrophy has become clear; indeed, acute yellow atrophy has been practically transformed from an obscure disease into no distinct and separate disease at all, but a severe and striking stage of a process that occurs in varying degree in various circumstances, and that appears clinically to be a distinct disease only when the autolytic changes become so severe and progressive as to be the reigning process. We have reason to hope that this conception of acute yellow atrophy will guide us to work out clinically much more clearly the early stages of the condition and its exciting causes, and ultimately may help us to intervene effectually at a period when dangerous lesions have not yet occurred. I think that we may have similar hopes in such conditions as recurrent vomiting, probably in the pernicious vomiting of pregnancy, in intoxications following anesthesia and in some other disorders, distant though the consummation of such hopes may be. Indeed, the studies made by Howland and Richards, which are highly suggestive in a number of ways, have already furnished some important practical suggestions as

to what should be done and what should not be done in the avoidance of the intoxication following anesthesia and to some extent in the treatment of this condition when it has actually appeared.

METABOLISM OF INORGANIC SUBSTANCES.

Another broad field that is only beginning to be cultivated in an understanding way is the metabolism of the inorganic substances found in the body. We know as yet very little in regard to this subject that can be used in any clinical way, but the remarkable researches of Jacques Loeb especially have led to information regarding its importance in elementary physiologic processes, particularly in the lower forms of life. His work makes it evident that it must come to have highly important clinical relations, and the studies of Alonzo Taylor of the effects in the human being of a salt-free diet are sufficient evidence of the profound effects that alterations in salt metabolism may produce and of the clinical interest that attaches to investigations of the physiology and pathology of this question. Various other studies are likewise extremely suggestive in this relation and the marvelous effects of the antagonism between calcium and magnesium that Meltzer has demonstrated make the developments in this field of still more intense and immediate importance.

CONCLUSIONS.

The actual clinical bearing of all these things that I have mentioned in this latter portion of my remarks still lies chiefly in the greater breadth that they have given us in our conceptions of the nature of normal and diseased processes. Their direct bearing on such practical things as diagnosis and treatment is slight. But we can not ask that clear and especially that comprehensive clinical relations should yet be evident. They touch so closely on the things fundamental in understanding life itself that to ask that their bearings shall all be made clear in the span of a man's life is equal to asking that in the same period of time all the world shall reach that "far off divine event to which the whole creation moves." But, as I have indicated, we shall be able gradually to accumulate a few facts here and there that will be directly available in practice if the proper principles are followed, even though obscurity still surrounds most of the details, and at any rate broad conceptions that lead to a more correct general line of action are, all in all, more valuable to the clinician than are a few detailed additions to our direct diagnostic and therapeutic methods, even though these additions accomplish their special purposes very effectually. In witness of this I would mention the great value, on the one hand, of a general comprehension of the influence that can be

exerted in the prevention and cure of many infectious diseases, for instance tuberculosis, through general measures directed toward increasing the resistance of bacterial growth and toxin action; and, on the other hand, the relatively slight importance in the general course of practice of those details that have been developed regarding the scientific special treatment of most such special infections.

I have pictured a very incomplete and hasty view of the relations between metabolism studies and clinical medicine. If I am criticized, as may readily be done, for having made my attitude toward my subject one of championship rather than of exposition, I would say that I have done this deliberately, for I feel that, in past years especially, and to a large extent even now, the teaching of subjects that bear on metabolism has, much more than is the case with most other subjects in medicine, been such as to give some knowledge of details and methods, but not such as to give a comprehension of the philosophy of metabolism studies in their bearing on clinical conditions.

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CANCER PROBLEMS.*

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Cancer research to-day includes three separate departments:

I. The Parasitic Theory.
II. The Theory of Cell Autonomy.
III. The Modern Biologic and Biochemic Study of Tumors.

I. THE PARASITIC THEORY.

Since the seventeenth century, and the time of Lusitanus, medical literature has contained numerous reports of the contagiousness of cancer. It has been claimed that the disease arises in epidemics; that it is increasing in frequency; that it exhibits, in certain localities, a significant relation to the soil and water; that it is transferred from one human being to another; that it may be inoculated into lower animals; while many have claimed to have identified the parasitic cause of its contagion.

Endemic Occurrence of Cancer.—The observations on the endemic occurrence of cancer, under current discussion, relate to the discovery of many tumor animals in the stock of one breeder, to the frequency of cancer of the eyelid in certain herds of cattle (Loeb[1]), to some peculiar cases suggesting cage infection among laboratory animals (Borrel,[2] Loeb,[1] Gaylord[3]) and, finally, to remarkable forms of epidemic cancer occurring among fish (Plehne,[4] Pick[5]). A careful examination of all these records shows that cancer may occur with remarkable frequency among aged, domesticated animals, but none of the above writers, except Plehne and Pick, have adduced any evidence which even strongly suggests an infectious origin of cancer. Similar evidence may be found to prove the infectious nature of eclampsia, diabetes, and insanity.

Cases suggesting cage infection are extremely rare. Bashford saw nothing of it in his experiments with 30,000 mice housed under conditions extremely favorable for the natural transfer of any contagion in mouse tumors. The occurrence of several tumors among the mice of one breeder is explained by the fact that the great majority of these tumors are cancers of the breast in old females long used for breeding. Other suspicious cases may safely be referred to the influence of inbreeding, old age, and uniform reaction to environment.

* A lecture delivered before the Harvey Society at the New York Academy of Medicine, Nov. 16, 1907.

The cancers among fish are more significant, and their origin is not yet entirely clear. Pick has shown that thyroid cancer in artificially bred salmon trout has, in one year, carried off 7 per cent. of the fish in the Auckland Society Trout Hatchery, while Bonnett[6] reported as many as 3,000 cases in one hatchery within four months. Only the older fish, 2 years and over, were affected, the younger ones being practically immune. In the same hatchery one variety, *Salmo fontinalis,* may be affected, while another, *S. iridescens,* may be entirely exempt. Such facts render highly improbable any parasitic factor in the origin of this disease, and Pick concludes that inbreeding and the chemical peculiarities of the water induce, first, simple goiter in large numbers of the animals, many of which later become cancerous. Likewise with "carp-pox" Plehne finds no grounds for assuming an infectious origin, but attributes the epidemics to the results of inbreeding and local factors which intensify the influence of heredity to a degree not seen in any other conditions prevailing among animals.

Cancer is said to be increasing in frequency and appearing at earlier periods of life, and some find herein evidence favoring the parasitic theory. Yet Riechelman[7] has shown that in Berlin 20 per cent. of those dead from cancer come to autopsy without a diagnosis having been made, and a proportionate increase in the cases of cancer may still be expected from improved diagnosis. Another source of increase may probably be found, as shown by Newsholme,[8] in the lessened mortality from infectious diseases, especially in infancy.

A relation between the incidence of cancer and the character of the soil has been discussed by many writers. In England, Haviland[9] found the disease especially frequent on the alluvial soil along the banks of rivers and rare in the older limestone regions. Behla[13] has recently brought together many interesting facts which, he believes, indicate that cancer is a water-borne disease. The occurrence of cancer-houses has been urged by Arnaudet,[11] d'Arcy Power,[12] and Behla,[10] in favor of the parasitic theory. In recent years observations, impressions and arguments of this class have failed to maintain the interest they formerly aroused. Some of the fallacies of this line of argument have been clearly pointed out by Sticker[14] and by Prinzing.[15]

Is Cancer Inoculable?—If cancer can be transferred from one human being to another, then one of the essential characters of an infectious process will be demonstrated. No experimental evidence is needed to show that a malignant tumor may often be grafted from one part of the patient's body to another, since the several recognized modes of metastasis daily demonstrate this process. Hahn,[16] Cornil[17] and others

have needlessly performed inoculations in human beings without contributing any important scientific information, while to-day such experiments are being successfully performed on animals for legitimate objects in many laboratories.

That cancer may be transferred spontaneously by contact from a cancerous surface to an apposed abraded or inflamed surface in the same subject also appears to be a fact, but the cases demonstrating such an event in man are extremely rare. In order to demonstrate such a transfer, it must be demanded that the transferred tumor shall exhibit a structure similar to that of the original, but different from that spontaneously arising in the infected tissue. Epithelioma arising at the same point on the upper and lower lips always offers the possibility of the spontaneous origin of both tumors. It is extremely difficult to find a reported case, free from reasonable objections, demonstrating the transfer of cancer by contact of external surfaces. A typical but still uncertain instance is the case of Hartmann and Lecene[18]—that of a cylindrical cell cancer of the uterine cervix with cylindrical cell cancerous ulcer of the adjacent vaginal mucosa. As the vaginal ulcer did not show the usual type of squamous cell epithelioma, the authors concluded that the growth must have been inoculated from the cervix. Yet there are several types of cancer of the vagina, and some, especially those of plexiform arrangement, closely resemble cylindrical cell cancer. Moreover, the long duration of this case, four years, offers opportunity for metastases, for which the vaginal mucosa is a common seat. Yet the recent results of inoculation of tumors in lower animals render it highly probable that autoinoculation by contact of mucous surfaces may occur in man. One of the recognized modes of metastasis is through the passage of fragments of tumor along the esophagus or ureter (Butlin[19]) with implantation lower down in stomach or bladder.

Of much greater significance is the question of the inoculability of cancer from one human being to another healthy subject. Here the element of a comparatively refractory soil is introduced. The studies on tumors of lower animals show that this factor is of extreme importance, and they also show that the rules observed with one tumor and one animal can not be applied safely to other tumors and other animals. Hence the inoculability of cancer among human beings must be considered entirely from the observations on the human subject. The invariable immunity of surgeons to inoculation by the tumors on which they are operating has always justly stood as strong evidence that cancer is never spontaneously transferred from one human being to another. Alibert[20] inoculated five human cancers on himself and his assistants

with negative results. I am unable to find any satisfactory report of the transfer of a malignant tumor from one human being to another. The alleged cases of infection collected by Smith and Washbourn,[21] Park,[22] and Behla[13] demonstrate only the dominating influence of the preconceived notions of the observers, since many essayed to prove not only the communicability of cancer among human beings, but the frequent transfer of the disease from man to lower animal and from lower animal to man. It is noteworthy that observations of this class have largely disappeared from recent literature. The inoculability of warts appears to have been demonstrated by Lanz,[23] who produced a series of warts in the skin of his gardener's hand by implanting pieces of such growth taken from a human subject. Their genuine neoplastic nature may be doubted.

The cases of so-called "cancer a deux" have figured prominently, from time to time, but in none has the contagion been conclusively shown. Demarquay[24] collected 134 cases of cancer of the penis, in only one of which infection by coitus appeared possible. Of the twenty-seven cases of such infection collected by Guelliot[25] none are beyond question.

Is Human Cancer Inoculable in Lower Animals?—Among the very numerous attempts to inoculate lower animals with malignant tumors from human subjects, there have been for many years a small proportion of instances where the experimenter claimed success. The vast majority of such experiments have undoubtedly failed. Pianese[26] mentions twenty reports of failure by as many observers in a large total of experiments. Many others exist in the literature, and probably still other negative results have never been published. The alleged successful results have, with a few possible exceptions, not been able to meet the conditions required for a successful demonstration. Some of the exceptions appear to deserve mention.

In 1894 Boinet[27] inoculated sixty animals with fragments of human cancer, and in one case from a cancer of the penis and produced multiple nodules of the same histologic character in the peritoneum and along the spinal column. One may refuse to believe, but one can not successfully refute the genuineness of Dagonet's case,[28] 1904, in which the intraperitoneal inoculation in a white rat of a comminuted epithelioma of the penis was followed in fifteen months by voluminous tumors of the same histologic type in the peritoneum, spleen and liver. Dagonet's later cases (p. 552) were less satisfactory, as the alleged tumors produced were atypical and of different type from that injected. Leopold[29] also claims to have transferred a malignant tumor of the human ovary by intraperitoneal inoculation in a rabbit.

Jürgens,[30] in 1896-97, was quite sure that he had succeeded in trans-

planting human melanomata into rabbits. Werner[31] transplanted a human carcinoma of the jaw into an old dog, and claims to have seen the development of a genuine malignant epithelioma at the site of inoculation, with extensive metastases in the peritoneum.

While these isolated reports are inadequate to prove the occasional inoculability of human cancer in lower animals, they can not safely be discarded as mistaken observations. Orthodox opinion was once firmly set against the possibility of transferring cancer among lower animals of the same species. It would seem necessary, therefore, to regard the question of transference of human cancer to lower animals as undetermined, while urging that the weight of evidence is strongly against such a possibility. Metchnikoff and Grünbaum[32] failed in several attempts to transfer human cancer to higher monkeys.

That some cancers of lower animals may be distributed readily among members of the same species is one of the chief results of the recent experimental study of tumors, and the subject will be reserved for consideration later.

Certain malignant tumors having been shown to be inoculable, the question remains, what does this fact prove regarding the etiology of such tumors? The unreserved answer to this question must be that it proves nothing. Leyden[33] has ventured to claim that there is no distinction between inoculation and infection, and that the inoculability of certain cancers demonstrates their infectious nature and an extrinsic parasitic cause. It is, however, the most patent distinction between tumor metastases or inoculation and known infectious diseases that the new growth develops from the transplanted cells, from factors inherent in those cells, whereas all known parasitic micro-organisms produce lesions in which the cells are derivatives of the host's issue. In tuberculosis the infecting agent is the tubercle bacillus, while in cancer all available evidence points distinctly to the cancer cell as the infecting agent and the homologue of the tubercle bacillus. Borrel,[34] a consistent advocate of the parasitic theory, clearly accepts this distinction, and admits that the inoculability of cancer proves nothing for the parasitic theory, but claims that the continued growth of tumor cells does not disprove the existence of a parasite apart from the cells, a contention which need not here be disputed.

However important may be the studies so far reviewed for the general problem of the biology of tumors, it has long been evident that they have only a secondary and often a rather distant bearing on questions of etiology.

Recognition of the inadequacy of such evidence to solve the problem

has always led the advocates of the parasitic theory to attempt the direct demonstration of the parasite of cancer.

History of the Cancer Parasite.—The search for the cancer parasite has been a chaotic chapter in medical research. The investigators who have undertaken these studies have been of every degree of competence, and, inspired by the lively hope of results of sensational value, and guided by an imperfectly grounded theory, the majority seem to have substituted easy credulity for critical common sense and to have accepted vague suggestion as demonstrative proof. Hence it is little wonder that micro-organisms of every variety, according to contemporaneous interests, have at one time or another been widely accepted as the cause of cancer, even by experienced authorities of the highest standing. In the early nineties it appears to have been a question, not so much as to the infectious origin of cancer, but rather as to which of the many parasites was the real causative agent.

After the discovery of the specific agents in many infectious diseases, especially in the infectious granulomata, several observers claimed to have discovered specific bacteria in malignant tumors. These claims were with difficulty set aside, to be succeeded by an era, still continuing, of search for a protozoon cause of cancer. Later arose a tendency to attribute to blastomycetes an etiologic relation to malignant tumors, and, lastly, some have urged the claims of mycetozoa. A partial list of the various structures or micro-organisms at one time heralded as the cancer parasite, with name of author and date of publication, follows:

CANCER PARASITES.

BACTERIA: Bacillus of Rappin,[35] 1886; Scheurlen,[36] 1887; Francke,[37] 1888; Lampiasi,[38] 1888; Koubassof,[39] 1889.

Micrococcus neoformans, Doyen,[40] 1902.

COCCIDIA: Coccidium of Darier,[41] 1889; Albarran,[42] 1889; Thoma,[43] 1889; Sjobring,[44] 1890.

Coccidium sarcolytum, Adamkiewicz,[45] 1892; Soudakiewitsch-Metchnikoff,[46] 1892; Monsarrat,[47] 1905.

SPOROZOA (unclassified): Bird's eye inclusion, Foa,[48] 1891; Plimmer's bodies, 1892.

Sporozoon, Ruffer,[49] 1892; Sawtschenko,[50] 1893.

Amœba-sporidium, L. Pfeiffer,[51] 1893.

Rhopalocephalus carcinomatosus, Korotneff,[52] 1893.

Sporozoon, Kourloff,[53] 1894; Bosc,[54] 1897.

Hematozoon, Kahane,[55] 1894.

Cancriamœba macroglossia, Eisen,[56] 1900.

Leydenia gemmipara, Schaudinn,[57] 1896.

Intranuclear parasite, Schuller,[59] 1901-4.

BLASTOMYCETES: *Saccharomyces neoformans*, Sanfelice,[60] 1896; Plimmer,[60] Leopold,[61] Roncali,[62] Bra.[63]

Russell's fuchsin bodies.[63 1]

Mucor racemosus, Schmidt,[64] 1906.

MYCETOZOA: *Plasmodiophora brassicae*, Behla,[65] Podwyssoski,[66] Feinberg,[67] Gaylord,[68] Robertson and Wade.[69]
SPIROCHÆTÆ: Gaylord,[70] Calkins,[71], 1907.
Cyanid-fast bodies, Robertson,[72] 1907.

In reviewing this list it must not be supposed that the claims of these various pseudo-parasites were urged without abundant evidence of a certain type. Many of the observers believed they had isolated their micro-organisms in pure culture and had produced tumors with the cultures. The entire realm of zoology and botany was laboriously searched for parallel protozoon or vegetable forms, and few of the investigators ventured to announce their discoveries without the endorsement of some distinguished biologist. Many years of systematic and toilsome study were devoted by some observers, notably Sanfelice, to the support of their beliefs. One may well pause, while viewing this battleground, to acknowledge that no other problem of medical science has resisted such strenuous efforts directed toward its solution.

At the present day it can not be said that much of positive value remains from the search for the cancer parasite. Pathologic anatomists, who are most occupied with the nature of the tumor process, have seldom actively engaged in this search on account of objections to the parasitic theory, and in their opinion its results have been wholly negative. No parasite has yet been discovered in cancer.

The occurrence of peculiar cell inclusions in malignant tumors had long been known and interpreted as a feature of cell degeneration before the parasitic theory came into prominence. Virchow,[73] among others, so interpreted many of these bodies and warned against the hasty conclusions regarding them by adherents of the parasitic theory. Russell's fuchsin bodies were early described by Fox[74] and later by Klein,[75] and Lubarsch[76] in 1892 showed that they are present in many normal tissues. Darier's psorosperm of Paget's disease was openly repudiated by its discoverer in 1904.[77]

Among enthusiastic exponents there has never been the slightest approach to unanimity of opinion regarding the identity of the true parasite, its unity or multiplicity, its position in the cytoplasm, nucleus or intercellular spaces, nor as to its biologic position.

Stroebe,[78] reviewing the basis of the parasitic theory at the height of its popularity, 1894, found almost as many different parasites and theories as adherents of the theory, presented the views of seventeen open sympathizers with the theory who could not find sufficient evidence in its favor, abstracted the reports of many competent and some very experienced observers who pronounced against the parasitic nature of all cancer bodies, and with Lubarsch pointed out a score of degenerative

processes in tumor cells which certainly contributed to the numerous class of cell inclusions, and, in all probability, fully accounted for their occurrence.

By a process of attrition in the hands of friends the possible parasitic forms were reduced to a single body—the "bird's-eye inclusion"—first described by Langhans and correctly interpreted in 1886. Feinberg,[67] urged by Leyden, made a final effort to detect in this body and its supposed derivative, the Russel fuchsin body, morphologic characters demonstrating its parasitic nature, but Feinberg's criteria, double contour, nucleus surrounded by a clear zone, and metachromatism, were promptly and authoritatively discarded by O. Hertwig,[79] and Lubarsch[80] pronounced these characters to be positive evidence of a degenerative product. Foa, who first cautiously emphasized the importance of the bird's-eye inclusion of cancer cells, abandoned his belief in its parasitic nature at the Fourth International Medical Congress in Rome.

In this condition the question of intracellular parasites in cancer remains to-day, and one must subscribe to the conclusion of Lubarsch,[80] 1902, that no specific micro-organism has been demonstrated in cancer or in any other autonomous new growth.

In regard to the relation of mycetozoa to cancer, it must be urged that, according to von Tubeuf,[81] the histology of club-root, the disease of plants produced by *Plasmodiophora brassicæ*, is not that of a true neoplasm, the tumor resulting principally from distension and degeneration of infected cells surrounded by an area of inflammatory overgrowth; that the behavior of *Plasmodiophora* in plants is widely different from that of any suspicious structure in malignant tumors, and that the resemblance between the spores of *Plasmodiophora* and the bird's-eye inclusion is both affirmed and denied, while a resemblance does not assure identity.

With regard to blastomycetes, the researches of Busse,[82] Rabinowitch,[83] Sternberg,[84] Richardson,[85] Nicolls,[86] and many others have established the following conclusions:

1. Blastomycetes are rarely cultivable from protected tumors, but when present and living there is no ground for supposing, as does Sanfelice, that they can not readily be demonstrated by culture.

2. In sections of tumors, blastomyces, or structures resembling them, are not always present, and the identity of Plimmer's bodies or Russell's fuchsin bodies with blastomyces living (Plimmer) or dead (Sanfelice) has not been established, but has been rendered improbable.

3. When present in tumors the number and distribution of yeasts do not favor the belief that they have any essential relation to the tumor, but

rather that they represent a secondary infection only (Mafucci and Sirleo,[87] Meser[88]).

4. Elaborate studies of yeasts from many sources have failed to show any that are capable of producing tumors, and few that are pathogenic for animals, and have fully determined that the pathogenic action strictly attributable to them falls within the limits of an inflammatory process. A possible exception to this statement may be found in the results of Schmidt,[84] who is said to have produced a genuine malignant tumor by injections of a yeast, *Mucor racemosus*. His results have not been verified.

Spirochetes in Tumors.—Some interest has been excited by the discovery by Gaylord[70] and Calkins[71] of a single type of spirochete, in ten consecutive cancers of the breast, in mice obtained from three different localities, and in all of sixteen transplanted tumors from these strains. Gaylord found these organisms in the connective tissue and between the tumor cells of the growing edge, and he reports that the more virulent tumors contained the greater number of organisms. Borrel[89] had previously reported the discovery of many spirochetes in two mouse tumors, without attributing to them etiologic significance, and Wenyon[90] has shown that mice are susceptible to blood infection by spirochetes. Tyzzer[91] has given the clue to the interpretation of these results by finding several tumors in mice free from spirochetes, and by discovering large numbers of spirochetes resembling the spirochete of Gaylord in the organs and mediastinum of two mice dying several weeks after unsuccessful inoculations with tumors containing spirochetes.

In human cancers Mulzer[92] and Lowenthal[93] found spirochetes on ulcerating surfaces. In a series of thirty-five human tumors and twenty-five in the dog, I have found spirochetes only on ulcerated surfaces or in necrotic areas. By treating their tumor growths with KCN Gaylord and Clowes have succeeded in passing their infected mouse cancers through several generations entirely free from spirochetes. It appears, therefore, that spiral organisms must be added to the list of occasional saprophytes occurring in tumors.

Acknowledging complete failure to discover a specific parasite in cancer, some exponents of the parasitic theory are endeavoring to support the theory by collateral evidence, which is largely histologic. This interesting line of inquiry is, in the minds of many, a promising field, and it must be admitted that its evidence is far more direct than that derived from observations on the general occurrence of cancer. The results of this work are effectively presented by Borrel.[34]

It has been shown that the cell inclusions of cancer have homologues

in many other diseases which are highly infectious. According to Borrel, the psorosperm of Darier,[41] the cancer inclusions of the common types, the vaccine bodies of Guarnieri,[94] the intracellular bodies of *molluscum contagiosum,* and those described in *clavelée* by Bosc,[95] in the contagious epithelioma of birds by Michaelis,[96] in carp-pox by Lowenthal,[97] and in trachoma by Halberstädter and Prowazek,[98] are all cellular degenerative products which, however, are specific for these diseases and indicate a common type of etiologic agent. The real infecting agent Borrel[99] believes he may have discovered in the contagious epithelioma of birds in the form of a *congeries* of minute cocci staining by Loeffler's flagellar method and forming a mass lying beside the specific cell inclusion. Lipshütz[100] has described the same minute bodies in the filterable virus of *molluscum contagiosum,* and Burnett[101] in a human case, while Borrel[102] identifies them in vaccinia.

It is too early to draw conclusions regarding the significance for the contagious epithelioses of these interesting observations, but there need be no hesitation in pointing out the fundamental differences between the contagious epithelioses and true cancers. Besides the patent differences in gross and microscopic appearance of the lesions, in the clinical courses which vary from malignant variola to a chronic cancer lasting for many years, in the immunity promptly established in the epithelioses, and in the filterability of their viruses, all the infectious epithelial processes lack that capacity for limitless infiltrative growth which is just the essential and mysterious feature of malignant tumors. To assume a relation between cancer and any of these contagious epithelioses is to introduce an ill-founded hypothesis, which renders extremely uncertain the value of results obtained in this field.

It is not necessary, however, to deny all relation between parasites and malignant tumors. In one sense certain well-known micro-organisms seem to act as indirect exciting agents of tumors. One of the most important facts in the etiology of tumors is that many malignant neoplasms develop after long-continued inflammation which is caused by external irritants or parasitic micro-organisms. Inflammatory hyperplasia passes by insensible gradations into a neoplastic growth. Epithelioma of mucocutaneous junctions is usually the sequel of chronic irritation; cancer of the breast is generally preceded by chronic mastitis; hypernephroma often by renal calculus; cancer of the stomach by simple ulcer. Considering the frequent development of epithelioma after lupus or tuberculosis of the skin, and of sarcomatoid hyperplasias of lymph nodes in tuberculosis, it might be said that the tubercle bacillus is in one sense a cancer parasite, since in some cases it has a special ten-

dency to induce neoplastic hyperplasia. But at some point in the course of the cellular hyperplasma the tubercle bacillus gradually or suddenly disappears from the field and the tumor process continues from its own intrinsic forces. In the same way *Spirochæta pallida* seems to have a peculiar tendency to favor the development of epithelioma of the tongue after syphilitic psoriasis, but the spirochete does not follow the invading epithelial cells.

In the lower animals there are examples of neoplasms in which the continued presence of a parasite is more essential to the progress of the tumor, as in the coccidiosis of the rabbit's liver, in the vesical cancer following Bilharzia disease, and in the tumor-like processes produced experimentally by certain yeasts (Schmitt).

In none of these conditions does the parasite seem to act directly in producing the tumor as it does in causing its specific inflammatory reaction, but the tumor develops as a late sequela, from secondary factors set up by the long continued growth of the parasite. Adenoma of the liver follows coccidiosis only after protracted distension of the bile ducts.

Now it is fully recognized that the initiation of a tumor process is an entirely separate problem from its perpetuation when once established. We already know of many external irritants and micro-organisms which are concerned with the inception of tumors, but human ingenuity has so far failed to find any trace of an external irritant or parasite continuing throughout the course of a malignant neoplasm.

These considerations would lead one to conclude that external irritants and parasites are concerned only with the inception of tumors, and then indirectly; they suggest that certain irritants and parasites may be peculiarly effective in producing tumors; they suggest that in some tumors, especially in lower animals, neoplastic hyperplasia may depend in varying degrees on cellular irritants; they leave the way open for the discovery of new irritants and parasites concerned with the beginnings of tumors; but they shut the door against the theory of a special cancer parasite and of the necessity of a continuous irritant propagated by a micro-organism throughout the course of a malignant tumor.

II. THE THEORY OF CELL AUTONOMY.

The theory of cell autonomy is the product of the best thought on the nature of tumors, and in the minds of many offers a virtual solution of the problem. It is a growth from many sources and is greater than the mind of any one contributor to it, being firmly founded on the sum total of clinical observations and supported by assured principles drawn from many collateral sciences. It is not a finished theory, but has an

ever-broadening scope determined by the progress of the sciences on which it is founded.

It is not a popular theory, being difficult of comprehension in many of its phases, requiring concentrated study for its full understanding, and long familiarity for the proper appreciation of its force. The longer one studies it the more satisfactory it becomes, and this conviction lies at the bottom of the antagonism which pathologic anatomists feel for any theory or research which ignores its significance.

The germ of the theory of cell autonomy appeared in the studies of Remak[1] and Thiersch,[2] who traced the antagonistic relation of epithelium and connective tissue throughout embryonal development and detected its significance for the problem of cancer. Epithelium seemed to be everywhere the dominating embryonal tissue, and in the formation of organs seemed to cease growing when it met sufficient resistance from the connective tissues. Thiersch found in the weakening of membrana propria and stroma in the atrophying breast a relief of tension capable of reawakening the formative tendencies of gland cells, with their longer span of vital activity, and thus cancer developed. The decay of the connective tissues he regarded as senile involution and the growth of cells as degenerative proliferation.

The idea of cell autonomy appears more clearly in Cohnheim's theory. The groundwork of this theory had been laid many years before in the observations of Lobstein,[3] Remak, Thiersch, and Waldeyer,[4] and the theory was first definitely stated by Durante,[5] who in 1871 demonstrated that the cells of pigmented moles giving rise to malignant sarcomata are of embryonal type, whence he concluded that all tumors arose from embryonal cells. Cohnheim[6] in 1874 collected many facts regarding the large class of mixed and heterologous tumors, contending that they arise from masses of complex or simple tissue misplaced during embryonal development. Cohnheim believed that tumors also develop from small groups of cells which have retained their embryonal characters, but need not necessarily be misplaced. The idea of the embryonal character of the cells appeared to him essential. He believed that most of the embryonal cells result from over-production, chiefly at the period when the definite rudiments of the viscera are being formed from the germ layers, and he suggested that the superfluous cells were either distributed throughout the tissues or were gathered in groups at certain points, such as the mucocutaneous junctions. The sudden development of the cells into tumors he referred chiefly to changes in the blood supply.

The entire group of mixed tumors and the simple heterologous growths illustrate the basis of Cohnheim's theory. When one explores

the group of teratomata there seem to be all transition stages from the complex sacral teratoma containing parts of the gastrointestinal tract, respiratory and nervous systems, up to abortive parasitic implantations containing parts of organs or limbs, and even up to such phenomena as the Siamese twins. Likewise, when one passes downward through the complex heterologous tumors of the parotid to the simple heterologous growths which arise from small groups of cells misplaced in later embryonal life, such as adenoma of a supernumerary breast, it seems but a step to regard carcinoma of the breast as arising from embryonal cells, misplaced or not, and the conception arises that the whole question of tumor growth is one of the mechanics of development. According to both Critzmann[7] and Beard,[8] the entire history of oncology from cancer to twins is explained by the inclusion at various times and to various degrees of one egg cell or primary germ cell in another.

Cohnheim's theory had two principal deficiencies. It assumed the existence of embryonal cells where they can not be demonstrated, and it failed to explain satisfactorily why the embryonal cells suddenly start on their neoplastic course. Later discussion has abandoned the hypothesis of embryonal cells as a necessary basis of tumors, and has endeavored to explain on other grounds why certain cells begin to multiply. Yet oncology still bears, and always must carry, the stamp impressed by the discovery of the fact that embryonal cells possess in unusual degree the essential factors in tumor development.

The majority of tumors, however, in fact, the most malignant, do not, so far as is known, grow from embryonal cells. On the contrary, there is good reason to believe that many tumors develop from adult cells. Yet, while the English commission has elaborately shown that cancer throughout the animal kingdom is pre-eminently a disease of old age, many embryonal tumors develop late in life. To account for the limitless growth of adult cells the theory of cell autonomy introduces the conception of tissue tension, which has been most fully stated by Ribbert.[10]

Ribbert endeavors to explain the development of tumors solely by the removal of certain cells from the influence of tissue tension by which their growth is normally restrained. He abandons Cohnheim's theory that the disturbed cells must be embryonal, claiming that the regenerative capacities of adult cells are quite sufficient to account for all the characters of malignant neoplasms. He has laboriously endeavored to produce tumors experimentally by separating adult cells from their connections, but without definite success, and he brings evidence to show that the inflammatory growth of connective tissue separating epithelial cells is the usual method of freeing from tissue tension the cells which

go on to develop tumors. In psoriasis of the tongue and early adenocarcinoma of the stomach he finds fibroblasts growing between the epithelial cells and snaring them off from their normal connections. In this form Ribbert's theory is supported by a host of observations. Indeed, as the misplacement of adult cells must be very frequent, Ribbert fails to explain why tumors are not more numerous, and in the minds of many he inadequately provides for the particular forces precipitating the misplaced cells into the malignant process. He also failed to explain the frequent development of malignant tumors where no such displacement can be supposed to exist, and he ignored the fact, pointed out by Hansemann, that cells which seem to remain in their proper relations may still show the morphology of tumor cells.

Recently Ribbert has modified and expanded his views in important directions. He abandons the idea that the cells must necessarily be misplaced, holding that cellular changes in the supporting connective tissue are sufficient to disturb the physiology of epithelium and incite a tumor process. Studying early carcinomata, he emphasizes the importance of the precancerous stage. Here the initial change is a proliferation of subepithelial fibroblasts, with the production of new tissue which disturbs the tension between epithelium and connective tissue. This proliferation is of inflammatory origin and may be referable to irritation by metabolic products or secretions of the epithelium. The epithelium then reacts, also by proliferation, but the growth follows the analogy of normal gland formation, while, owing to a process of adaptation to the abnormal environment and loss of function, the atypical structure of cancer results.

According to Ribbert, tumors grow out of their own cells exclusively, never from the cells in contact with them, and since at all recognizable stages the tumor cell series is isolated, it follows that the cells of origin are isolated. To account for the primary segregation of the originating cells, he accepts all the known forms of separation of cell groups during embryonal life. The observations of Borrmann,[11] Meyer,[12] Lubarsch[13] and others have shown that foci of isolated superfluous cells are vastly more frequent than was ever imagined in Cohnheim's day. He also appropriates a large number of structural anomalies without displacement of cells, which may be explained by reference to the history of phylogenetic and ontogenetic development. The peculiar locations and structure of a large number of tumors suggest spasmodic reversions to the anatomic conditions of prehistoric man or of other, once more closely related, animal species.

Thus, the fusion of multiple reniculi, in phylogenetic development;

the coalescence of multiple uteri and breasts; the reduction in length of stomach, intestine, appendix and colon; the loss of lymphoid tissue in the relatively narrow human cecum, and of the elimination of hair and sebaceous follicles in the face, etc., all lay a significant foundation for the atavistic growth of tumors in many organs. It would be a pity if the comprehensive view of the etiology of tumors which is revealed in the phylogeny and ontogeny of the human body were destined to be replaced by the crude conception of an invading parasite.

On this broad basis of embryonal misplacements, developmental history, and suppressed potencies, the theory of cell autonomy proceeds to consider the neoplastic growth of predisposed cells. In order to appreciate how far the theory can explain malignant tumors, one must examine more closely the factors entering into the conception of tissue tension.

Conception of Tissue Tension.—All the forces which control the multiplication of tissue cells and maintain the tissue in a physiologic condition are included in the idea of tissue tension. At least four such factors are known, three of which are recognizable as physical forces, while the fourth, more complex, can not be wholly identified as purely physical. These factors are:

1. Mechanical pressure of cells on each other.
2. The influence of specialized functions.
3. The distribution of nutriment.
4. Organization.

Under each of these heads belong important contributions to the theory of cell autonomy.

Mechanical Pressure of Cells on Each Other.—The theory of Thiersch emphasized the importance of the mechanical restraint of epithelium by the supporting connective tissue. This theory deals with one of the factors which may often favor the growth of tumors, but it is obviously incapable of being extended to all tumors or to adequately account for any. Mechanical pressure is a powerful factor in the spontaneous regression of tumors. Regressing tumors are usually surrounded by a connective tissue capsule, and Loeb[14] found that when he excised a portion of such a regressing tumor in a rat and replanted it in the same animal it immediately began to grow rapidly.

Influence of Specialized Functions.—The energies of cells are normally divided between proliferation and specialized function, between work and growth, both being limited by blood supply. In most organs certain groups of cells are set apart for growth, and from these are derived the more specialized functionating cells. Examples are the germ center cells of lymph nodes, the cells at the bases of intestinal villi, and

the basal cells of the epidermis, and it is just from these cells, subject to marked variations of the demands for growth, that tumors arise. It is clear that deficient demands for function on the part of derived cells would leave their energies unconsumed and further available for growth. These conditions surround the inception of cancer in the atrophying breast. Adami[15] has ably presented the general importance of this point of view, designating the tumor process as the cumulative "habit of growth replacing the habit of work."

It may be objected that there is no warrant for the assumption that actively functionating cells can suddenly turn their energies into growth. Yet the fact that they do so is prominent in the history of tumors, as in the carcinomatous changes in the actively functionating goiter and in many instances of inflammatory hyperplasia becoming neoplastic.

Oertel[16] has pointed out that excessive activity of one function is observed in degenerating cells, as in the paralytic hypersecretion of glands, and in the excessive secretion of bile in degenerating liver cells. He claims to have traced the development of cancer of the liver from degenerating liver cells, and justly supposes that if the specialized functions of degenerating cells may be performed in excess, then an excessive capacity for growth may be expected in such cells. His theory that tumor growth is a form of cellular degeneration has been held by Thiersch and Benecke,[17] is supported by many peculiarities in the history of tumors, and is a valuable working hypothesis.

Distribution of Nutriment.—A vast number of clinical and experimental studies has established the importance of blood supply both for the inception and progress of tumor growth and for the physiologic proliferation of cells. It is true that hyperemia alone does not explain tumors, but nutrition is one of the important elements in tissue tension, and when its distribution is disturbed one of the essential factors of tumor growth is provided. An explanation of the excessive capacity of tumor cells to absorb nutriment would unravel a great mystery in the physiology of neoplasms. An extremely important bearing of this factor has been found by L. Pick[18] in the relation of corpus luteum secretion to chorioepithelioma. In 1895 Marchand[19] found that in a large proportion of cases of this very malignant tumor both ovaries show hyperplasia and cystic distension of the corpora lutea. It has been shown experimentally by Fraenkel[20] that the persistence of corpus luteum cells is essential to the development of the placenta, and the conclusion at once arises that excessive activity of these cells is responsible for the destructive proliferation of the chorionic epithelium. Here we have an instance of a specific internal secretion presiding over the growth of an organ

and its excessive production associated with a malignant tumor of that organ. It has been objected that cystic ovaries are not always found with chorioepithelioma, but the theory need not fall on that account, while Patellani[21] finds that up to 1905, 91 per cent. of the fully reported cases of chorioma were associated with bilateral cystic ovaries.

The theory of specific internal secretions presiding over the nutrition of specific tissues has, possibly, a wide application in physiology, and this theory, combined with that of Cohnheim, with which it ranks in importance, may be found to cover a large group of malignant tumors. Ehrlich has applied the theory of a specific nutritive substance, not itself the nutritive molecule, but presiding over nutrition, to explain the interesting results of his zigzag transplantation of mouse tumors from mouse to rat and back.

Organization.—The most important element in tissue tension is that designated as organization. This is itself a complex conception, but in it we approach most closely to the true meaning of normal and of tumor growth, and here is found the most hope that a final explanation of the tumor process may be attained.

If the head and several segments of an earth worm are cut off, the body regenerates a head. If the leg of a crustacean breaks off, a new leg is regenerated at or near the breaking joint. If the head of a flat worm is cut off and the stump split for a short distance down the middle, two heads develop, if the split ends are held apart, but only one if the split ends coalesce. If the head of an earth worm is cut off, a new head develops, but if the severed head is immediately replaced it unites, no new head is regenerated and regeneration is suppressed.

If one removes the crystalline lens in Triton, the upper edge of the iris regenerates a lens; if the iris is removed, the chorioid regenerates a lens; if the chorioid is removed, the retina forms a lens. Three different specialized tissues develop a lens under the influence of a purposeful organization. Any part of the Begonia plant reproduces the entire plant, and a severed leaf of the flowering plant proceeds at once to produce flowers. If a severed branch of the hydroid, *antennularia*, is suspended in water, tip uppermost, twigs develop above, roots below, but if it is suspended tip downward, twigs replace the roots above and roots the twigs below. This hydroid possesses a certain polarity of organization which is slowly alterable by gravity. Tissue cells also possess a polarity of organization, especially lining epithelial cells, and it would be an interesting study to trace the influence of disturbed polarity in the inception of tumor processes.

Throughout these and many other experiments in the mechanics of

development it is evident that regeneration is controlled by the organization, and this, as Morgan[22] claims, can be defined only in terms of purpose, and can not be wholly resolved into any known physical forces.

Now, a tumor can be defined only in terms of purpose. All the features of a malignant neoplasm are exhibited by the normal decidua, even to the destructive invasion of organs and cachexia, but the process is not a tumor because of its purpose. Routine tumor diagnosis constantly involves the recognition of this fact, if errors are safely avoided. All of the above observations display, in clearer light, the meaning of the loss of organization in the regenerative processes in tumors. Yet experimental morphology has so far signally failed to elucidate the reason for the loss of organization in tumors. Much more definite results have followed from the study of cellular processes in development and regeneration.

The dividing embryo, up to the sixteen-cell stage, in some animals yields cells, any one of which, if separated from the others, is capable of producing an entire embryo. Beyond this stage, and usually before it is reached, the cells become differentiated, different cell groups going to produce different specific tissues. According to Weigert[23] and Roux,[24] this differentiation results from an unequal division among the cells of the properties of the mother cells, eventually of the ovum, under the influence of an inherent internal impulse of the mother cell. Here again in the cellular processes of development is encountered the purposeful force of organization. As the tissues are differentiated in the embryo, owing to the unequal distribution of qualities or potencies, some cells come to possess more of one type and others more of another, while the sum total of the potencies of all types is necessary to maintain the equilibrium of the organization. Any alteration, as in the number of one type of cell, must necessarily affect all other types in the organization, if there is to be equilibrium. Hence, the cells, tissues and organs stand in a relation of antagonism or correlation necessary to maintain the equilibrium of organization, any change in one affecting more or less all the others. This interdependence has been called by Hansemann the altruism of the cells. Removal of one kidney is followed by compensatory hypertrophy of the other through the physical factors of increased urea in the blood, increased blood supply and nervous stimulus, all acting harmoniously under the influence of the organization. There is altruistic hypertrophy of many bones following destruction of the hypophysis in acromegaly, and altruistic atrophy of the adrenal in anencephalic monsters. A definite chemical substance conveying this altruistic influence may be found in the corpus luteum secretion which controls the

growth of the chorion. The influence of the altruism of the tissues must be included in the conception of tissue tension.

Consideration of the internal processes in cell division also has important bearing on the question of organization and tumor growth. As long as the cells multiply by normal mitosis, and each stage of differentiation in one group is accompanied by equivalent antagonistic qualities in others, equilibrium is maintained. But if from the altered conditions occurring in inflammation, chemical or mechanical factors derange the mitotic process, single chromosomes may be destroyed, the resulting cells will not receive the ancestral qualities in normal proportion, and a new biologic type will result which will not have the proper antagonists to balance it. Such cells will then be thrown out of the organization, and if their posterity suffer the same disturbance of the mitotic process they will eventually fail to receive any restraining influence whatever from the organization.

By such a process the theory of cell autonomy supposes that malignant tumor cells develop. But, before accepting any of these hypotheses, it must be demanded that tumors show some tangible evidence in support of them. Such evidence is by no means wanting.

The general history of malignant tumors is most consistent with the view that they represent aberrant tissues which have lost the control of the organization. Especially when the influence of all the factors in tissue tension which controls the growth of cells is considered, a moral certainty is established that the theory of cell autonomy is substantially correct and adequate.

The study of cell division under many conditions offers strong support to the theory. Hertwig[25] has shown that by means of an external chemical stimulus by chloral hydrate a beginning mitosis may be suppressed and the nucleus return to the resting stage. When mitosis occurs later in such a cell it divides into four instead of two daughter cells. Hansemann's studies of tumor cells show that unequal, asymmetrical and multipolar mitosis and destruction of chromosomes is of frequent occurrence, especially in the more malignant tumors. Hansemann[26] applies the term anaplasia to the condition of such cells, and these appearances may now be understood as signifying loss of normal differentiation, specific function and organization. Anaplastic cells are, therefore, not embryonal cells, but a new type which have lost their place in the old organization. More or less anaplastic cells, with irregular mitosis, occur also in inflammatory processes, but this fact does not affect their significance in tumors. There are all grades of anaplasia as of malignancy of tumors: inflammatory hyperplasia passes gradually into neo-

plastic, and the fully anaplastic cell, capable of excessive growth, appears to be limited to malignant tumors.

In still another relation the study of cell division in tumors seems to have important bearing on the nature of the tumor process. In some animals the entire series of sexual cells, from the fertilized ovum up to the new egg cell, have been traced without a break. In this series the mitotic nucleus exhibits only one-half the number of chromosomes found in the somatic or general body cells, and these chromosomes, instead of assuming a V shape and radial arrangement, and splitting lengthwise in the monaster, are ring- or loop-shaped or composed of four coarse granules arranged in the long axis of the spindle. In higher animals the sexual cells are derived from the somatic cells by the gradual appearance of this type of mitosis, called "heterotype" or "gametogenous." These cells have very important altruistic relations in the organism, and in some insects their loss or the completion of their function entails death. Moreover, the sexual tissues may act as parasitic elements invading and destroying the somatic tissue as in the embryo sac in the ovule of a flowering plant, or as the syncytial cells in man.

Recently Farmer, Moore and Walker[27] have followed the development of heterotypic mitosis in the growing edges of epithelioma, and have found that this type of mitosis is common in this and other malignant tumors. Since tumor cells do not produce true sexual tissues, they apply the term gametoid to these mitoses in neoplasms. These observations support the view that tumor cells constitute a specific biologic series. Hansemann[28] claims priority in this conception, asserting that the same general ground is covered in his observations on mitosis in anaplastic cells. The two views have much in common and relate to identical objects, but Farmer, Moore and Walker have taken one abnormal type of mitosis in tumors and attributed to it an entirely different significance from anything which I can find in Hansemann's interpretation.

The cause of gametoid mitosis is still to be determined. Chemical irritants are able to produce it in plants, and Farmer, Moore and Walker attribute it to chronic irritation and other stimuli known to favor the development of tumors. Whatever its origin, observation teaches that it is chiefly found in anaplastic, lawlessly growing cells. Many criticisms of these hypotheses have succeeded in showing that tumor cells are not, because of their gametoid mitosis, equivalent to sexual cells, but they have not, I think, reduced the general significance of the fact that tumor cells and sexual cells now have three known common properties, heterotypic mitosis, destructive invasive properties, and striking altruistic relations.

The theory of cell autonomy claims, therefore, to have established the existence of a specific type of cell in malignant tumors, exhibiting the abnormal physiology and the peculiar morphology of anaplasia. The crucial question is whether the limitless power of growth of these cells has been explained satisfactorily. Ribbert emphatically insists that no unusual power of proliferation exists in cancer cells, that these cells freed from the restraints of tissue tension are merely exhibiting the powers of growth with which they are endowed from the ovum. He claims that there is no such thing as a malignant tumor cell endowed with new and prodigious capacity for multiplication, but that tumor cells and their normal progenitors are alike in this respect. In this view he is supported by Weigert and Roux, who claim that the regenerative capacities of cells are determined from the moment of their derivation from the ovum and can never be increased by any external stimulus, although they are constantly restrained by the organization. In one sense, it is difficult to escape from the conclusions of Weigert and Roux, since it is the fertilization of the ovum which endows it with the particular organization and regenerative powers necessary to produce the adult organism, while fertilization of the new sexual cells is again necessary before new regenerative powers arise and produce a new organism. Recognition of this difficulty has led many to suppose that tumor cells are really fertilized cells, through conjugation with leucocytes (Klebs[29]), or by some form of parthenogenesis (Waldeyer[30]), or by conjugation of endothelium and fibroblasts (Recklinghausen[31]), or by nuclear conjugation of equivalent cells (Auerbach,[32] Bashford[33]), or by endogenous cell infection (Schleich[34]).

All observers have not accepted the Weigert-Roux hypothesis. Lubarsch finds it incompatible with the facts of metastases of malignant tumors, and claims that external stimuli may induce an enormous increase in the regenerative capacities of cells. It might be supposed that the excessive growth of tumor cells is merely an expression of an excess of regenerative power produced from the ovum as an increment of safety, in the sense of Meltzer.[35] But tumor growth far surpasses any limit of safety. Ehrlich[36] has computed the enormous bulk of mouse tumor which has been produced from cells of the Jensen strain, and it is conceivable that most of the earth's nitrogen might be converted into mouse tumor if only there were enough cancer laboratories. R. Hertwig,[37] J. Loeb,[38] Calkins,[39] Schucking[40] and others have shown that the growth of cells, protozoon and metazoon, may be enormously increased by changes in the environment, and their observations as well as the history of

tumor growth speak, in the judgment of many, against the Weigert-Roux theory.

The organized regenerative properties of tissue cells are truly determined in the fertilized ovum, but the mere *power of multiplication without organization* is subject to infinite variations from the influence of the environment, and, as has already been shown objectively, tumor cells may apparently grow forever.

We see, therefore, that the growth of tissue cells is normally controlled by the organization, that these cells possess regenerative powers greatly in excess of ordinary needs in order to meet extraordinary and accidental requirements, and that cells exhibit, in response to certain external conditions which some call stimuli, enormous grades of proliferative capacity. Why limitless growth should be such a striking characteristic of anaplastic cells which have lost the control of the organization we may not fully understand, but we can observe it as a fact.

The theory of cell autonomy, therefore, seems to adequately account for the phenomenal growth of tumors. It may be necessary to provide an external stimulus, but this necessity is not clearly apparent. So far as we know, the limitless capacity of tumor cells to absorb nutriment and grow may be an essential property of the protoplasm and organization of tumor cells, and beyond this descriptive knowledge we may not hope to penetrate.

Is the parasitic theory a valid possibility? An important bearing of this discussion lies in the fact that it opens the way for the parasitic theory, which, according to the Weigert-Roux hypothesis, is not a valid possibility.

In the light of the facts illustrating cell autonomy, we may consider, finally, to what extent the action of parasites in tumors can be regarded as possible. Abandoning all claims to the demonstration of a cancer parasite, it is maintained that a parasite is the only form of external stimulus that can account for the growth of tumor cells. The question is a very narrow one and admits of no obscurity. Can a parasite, growing with or within tumor cells, account for their lawless growth through endless generations, with the full preservation of their nutrition and vitality? It must be admitted that when the theory of an external stimulus is allowed, the possibility that this stimulus comes from parasites is also accepted. That a cancer parasite is a logical possibility must be acknowledged freely. We can not argue it out of existence from the nature of the tumor process. It may be shown, however, that it is unnecessary, unsupported by analogy, and inconsistent with the history of most tumors.

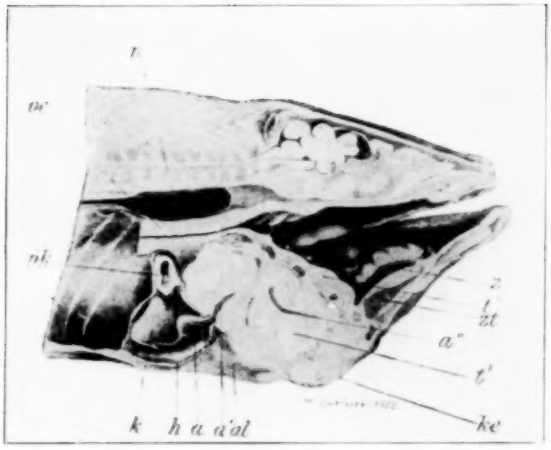

Fig. 1.—Thyroid carcinoma of trout (after Pick). a, a', a", Aorta. t', Tumor mass. t", Tumor invading pharynx. z, Tongue. k, Cardiac chamber. œ, Esophagus. n, Kidney. al, Compresser ventral muscle.

Fig. 2.—Adenocarcinoma of trout invading branchial arch (after Bashford).

Fig. 3.—Liver, spleen, omentum and microscopic section of Dagonet's transplanted human epithelioma in a rat.

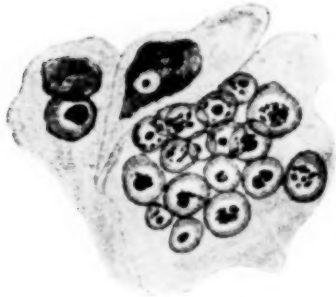

Fig. 4.—Cancer parasites (after Ruffer and Plimmer)

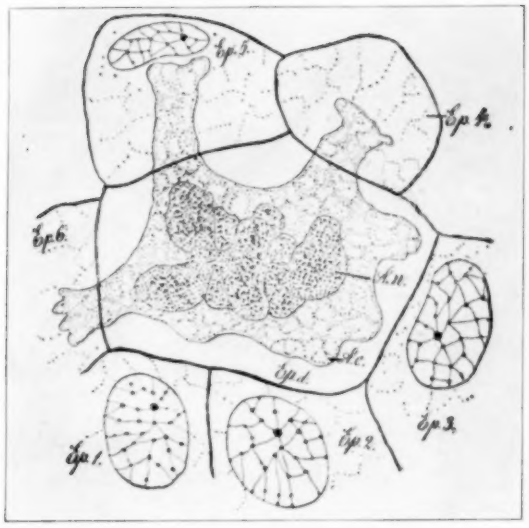

Fig. 5.—Cancriamœba macroglossia (after Eisen). A. c., Amœba. A. n., Nucleus of amœba. Ep. 1-6, Epithelial cells. Ep. d., Destroyed epithelium.

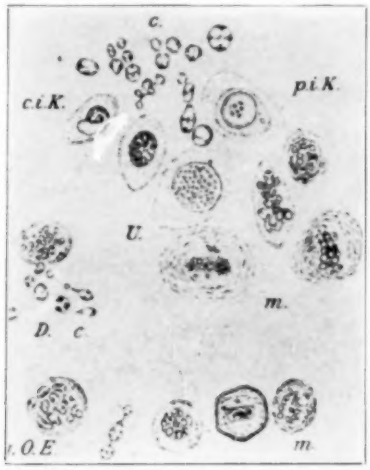

Fig. 6.—Schuller's intranuclear parasite of carcinoma and sarcoma. U, Uterine cancer. D, Intestinal cancer. p.i.K, Intranuclear parasite. c.i.K, Chromatin bodies in nucleus. c, Chromatin bodies free. m, Mitosis-like grouping of chromatin bodies. j.O.E. Young organisms.

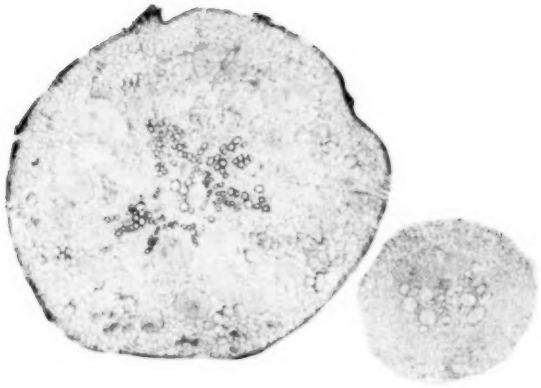

Fig. 7.—Normal and hypertrophic plant root infected with Plasmodiophora (after Woronin).

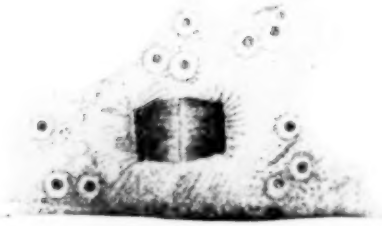

Fig. 8.—Dividing vegetable cell infected with Plasmodiophora.

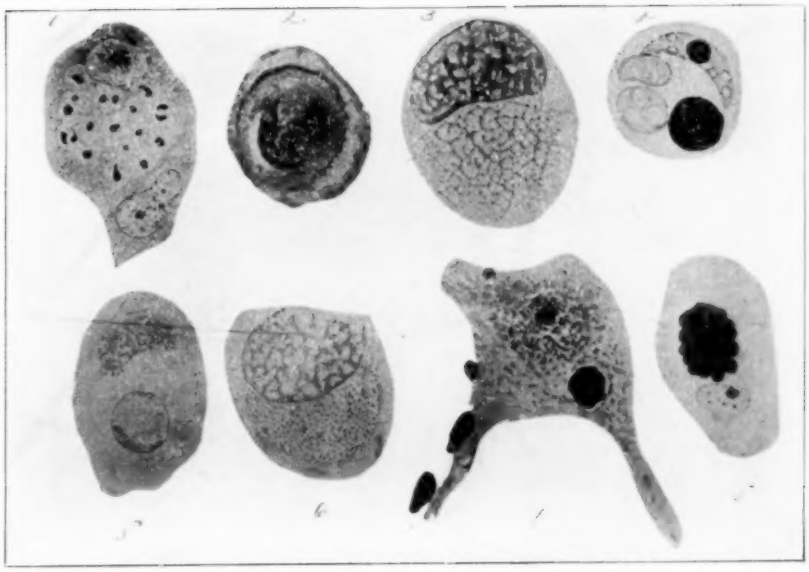

Fig. 9.—Intracellular bodies in the 'contagious epithelioses.' (Photo by Dr. Leopold Jaches.) (1) Cancer bodies (after Sawtschenko). (2) Molluscum contagiosum. (3) Vaccine body in Klaatsch preparation of rat's cornea (photograph of drawing). (4) Measles; intracellular bodies of cutaneous epithelium. (5) Clavellé (after Bose). (6) Trachoma (after Halberstädter and Prowazek). (7) Negri bodies of rabies (after Williams and Lowden). (8) Contagious epithelioma of birds (after Michaelis).

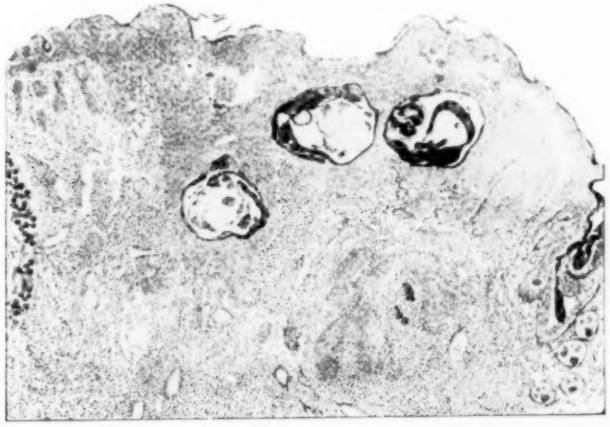

Fig. 10.—Epithelial tumor in ear of rat. Acari in Malpighian tissue (after Borrel).

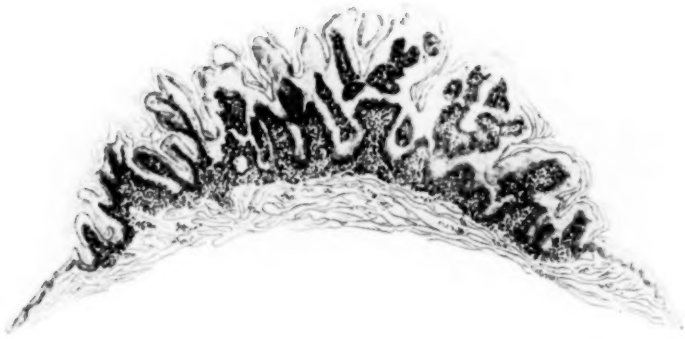

Fig. 11.—Beginning epithelioma of lip. Thickened epithelial papillæ over a layer of dense cellular infiltration (after Ribbert).

Fig. 12.—Choriocarcinoma, with bilateral cystic ovaries.

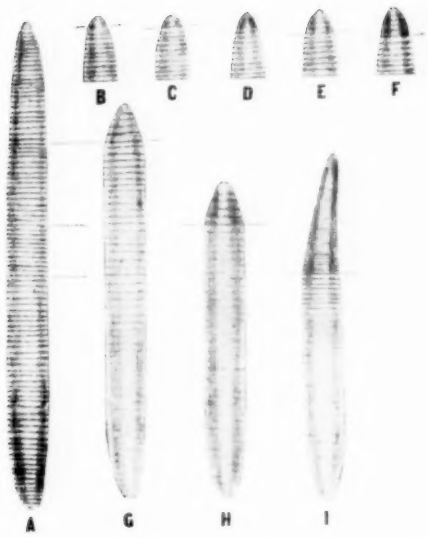

Fig. 13.—Regeneration in earthworm. A, Normal worm. Remaining figures indicate levels of section with resulting regeneration (after Morgan).

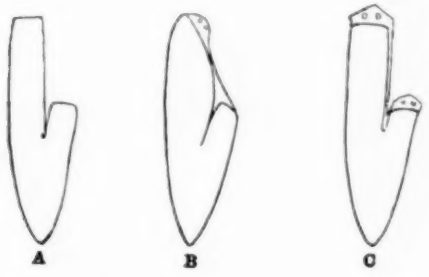

Fig. 14.—Regeneration in a planarian. A, Lines of section. B, Regeneration when divided ends coalesce. C, When divided ends are held apart. (After Morgan.)

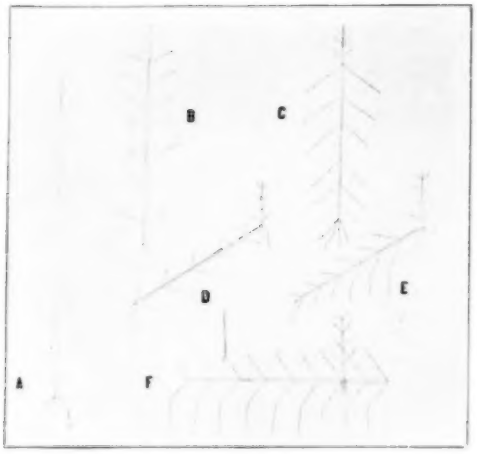

Fig. 15.—Regeneration in Antennularia (after Morgan). A, Normal growth. B, Growth of transplanted stem in upright position. C, In inverted position. D, E, In oblique positions. F, In horizontal position.

Fig. 16.—Achimenes Haageana. A leaf-cutting of a plant in flower. The new plant, regenerating at base of leaf-stalk, proceeded at once to produce a flower (after Goebel).

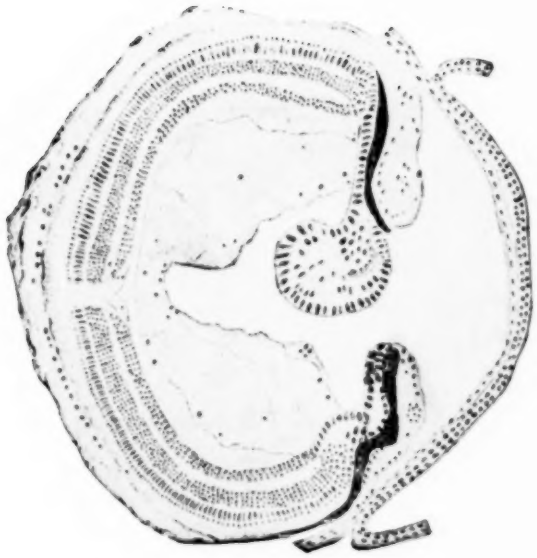

Fig. 17—Regeneration of crystalline lens in triton (after Morgan).

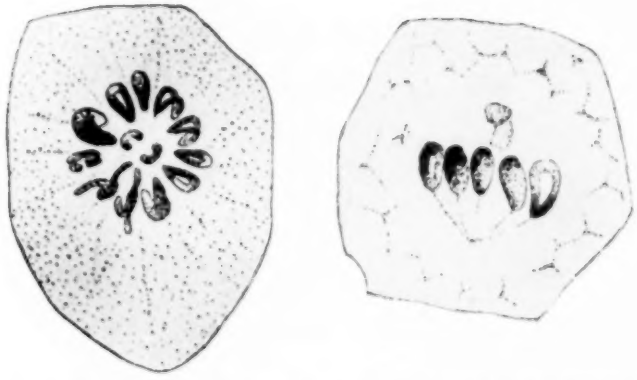

Fig. 18.—Heterotype mitosis in adenocarcinoma of trout (after Bashford).

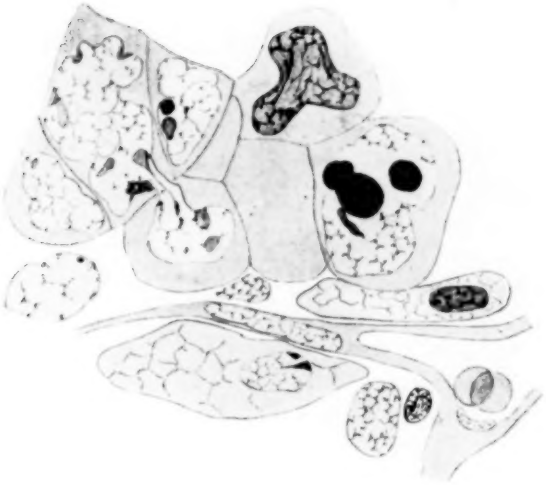

Fig. 19.—Conjugation of resting nuclei. The two nuclei of adjoining cells are continuous by means of a narrow tube-like neck through the cell wall. Note darkly-stained ameboid nuclei in upper part of section (after Bashford).

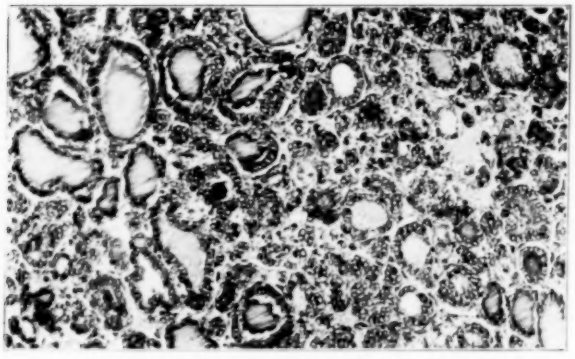

Fig. 20.—Adenoma of aberrant thyroid in dura mater. Case of Dr. F. M. Jeffries.

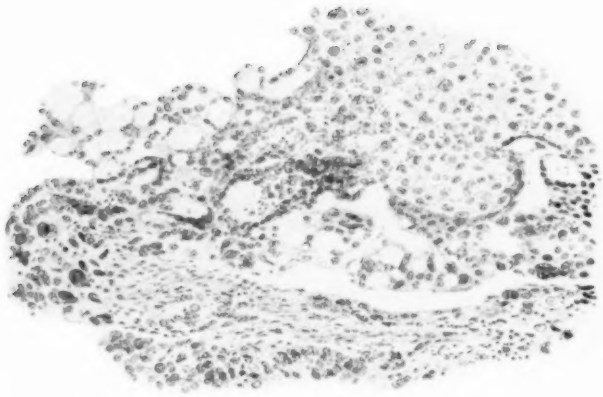

Fig. 21.—Chorioma of testis (after Schlagenhaufer).

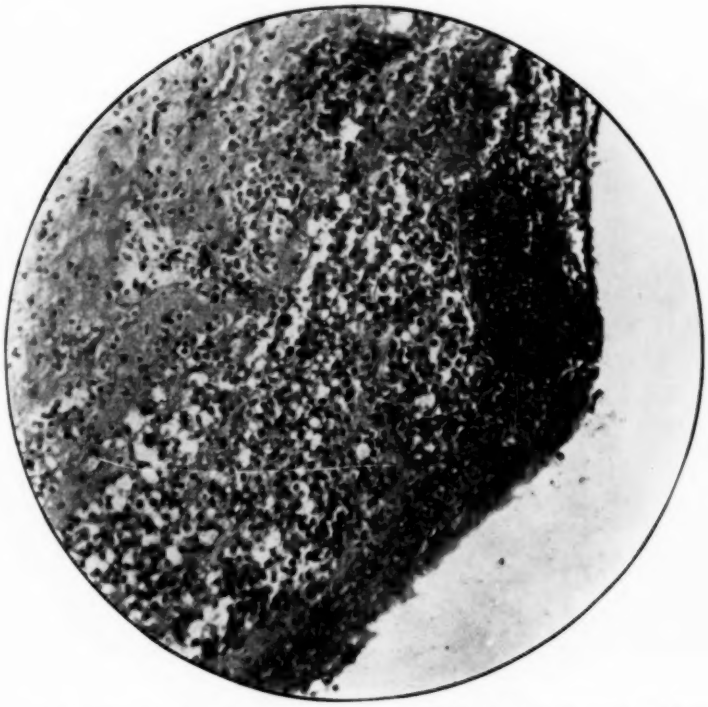

Fig. 22.—Lymphosarcoma of dog. Transplanted piece after twenty-four hours, showing zone of surviving cells. ×330.

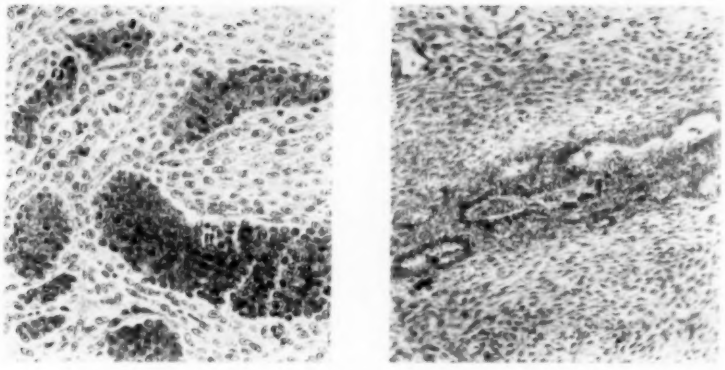

Fig. 23.—a, Mixed tumor of mouse (after Ehrlich). b, Human adamantinoma with fusiform epithelial cells resembling sarcoma.

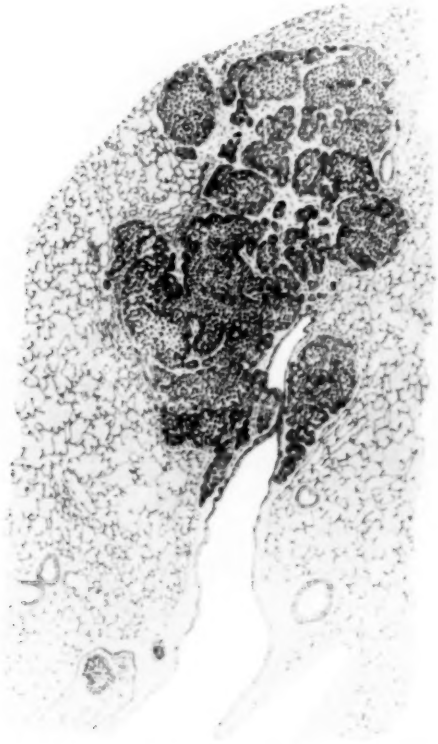

Fig. 24.—Transplanted carcinoma of mouse. Infiltrative and expansive growth of metastases in lung twenty-six days after intraperitoneal implantation (after Bashford).

When one considers the importance of Cohnheim's discovery of the embryonal character of the cells of origin of many tumors, the evolutionary significance of neoplasms, the influence of specific substances presiding over nutrition and growth of many tissues, the general altruistic relations of cells and organs, the enormous regenerative capacities of mechanically-injured cells in man and lower animals, the conclusion slowly but inevitably results that the destructive growth of tumor cells is adequately explained by the theory of tissue tension and cell autonomy, and that a parasite is unnecessary.

When one starts out to find in nature an analogue for the cancer parasite which, instead of destroying its host, stimulates its nutrition and vitality, one fails to find any example of such a form of parasitism, and one must eventually subscribe to the second conclusion of Lubarsch that nowhere in the animal or vegetable kingdoms exists any analogy for the cancer parasite.

In many details the parasitic theory is inconsistent with the history of tumors and tumor metastases. For the extensive group of teratomata and of mixed tumors of organoid character it is definitely inapplicable, since these growths exhibit the natural development of embryonal tissues, and if this is parasitic, then, as Wilms[43] points out, the whole course of embryologic development must be of parasitic origin. In a metastasis from an ovarian teratoma Lubarsch[41] found brain tissue and ependyma in orderly arrangement. The atavistic nature of chorioma of the testis is unmistakable. Metastases are not always simple embolic groups of growing cells. Many of them are distinctly organoid in character, maintaining definite polarity in cell arrangement, and functionating as organs. Strictly comparable with the simple heterologous tumors are the aberrant adenomata of the thyroid, which Ribbert believes can only be explained as the result of emboli of normal thyroid cells.

Multiple enchondromata of the epiphyseal cartilages and along the vertebræ, which are imperfectly-suppressed remnants of an old chorda dorsalis, show distinctly hereditary features and cease to grow when the skeleton is fully developed. Lipoma passing into liposarcoma is often clearly connected with an obese habit of the individual. Moles and cutaneous angiomata are congenital in origin and remain harmless until mechanically disturbed. There is no essential difference between any of these tumors, since all occasionally produce metastases.

There remain for the possible application of the parasitic theory only the simple homologous tumors, including, however, the important group of cancers. Yet with the exception of the lymphosarcomata, whose position remains uncertain, the most minute study has failed to show any

essential difference in the nature of cancer and the heterologous tumors.

Hopeless dilemmas seem to arise when one attempts to trace the necessary behavior of the cancer parasite. Some rare tumors, such as primary epithelioma or thyroid adenoma of bone marrow and hypernephroma in distant organs, require that the parasite pick out minute aberrant groups of cells in protected situations. Chorioepithelioma is one of the most characteristic and destructive of malignant homologous tumors. Its early phases, however, are with great difficulty distinguished from chorionic epithelium wandering within physiologic limits. It arises indifferently from uterine or tubal gestation or from hydatid mole. The adjacent maternal epithelium always escapes infection from any parasite in the fetal epithelium, although cancer of the uterus may arise during pregnancy. The various congenital sarcomata of the kidney very often develop *in utero* while the parents are free from demonstrable tumors.

Embryonal and misplaced tissue invaded by metastases fails to suffer infection. Hypernephroma frequently shows metastases in the healthy adrenal of the opposite side. Shaffer and Lubarsch[41] have described misplaced islands of gastric mucosa in the esophagus invaded by epithelioma of the esophagus, but showing no hyperplasia. Berent[42] has observed a misplaced adrenal in the kidney containing a metastatic nodule from epithelioma of the jaw, but without showing any evidence of proliferation. A bruised pigmented mole may produce widespread metastases in a few weeks, or ten years may elapse between the removal of the melanoma before the appearance of rapidly-growing metastases.

The cancer parasite, therefore, must invade minute groups of cells in protected organs, even in the embryo of an immune parent; it invades only the tumor cells and their derivatives, but not other tissue cells; infecting one embryonal cell it will not attack other embryonal cells in immediate contact; it induces destructive growth, ending in necrosis and fatal cachexia, or stimulates normal embryologic development with the production of comparatively typical tissues and organs; and it does all this with frightful rapidity in a few weeks, or it lies for ten years giving no hint of its presence.

The whole basis, objective and theoretical, of the cancer parasite has been traversed again and again, with the uniform conclusion by those who finish the journey that the cancer parasite is the cancer cell. We should, therefore, avoid the temptation of searching for an easy solution of the cancer problem and content ourselves with the more laborious but safer progress along the lines converging in the doctrine of cell autonomy.

III. BIOLOGIC AND BIOCHEMIC STUDY OF TUMORS.

During the past five years a new era in cancer research has opened in the study of transplanted tumors in lower animals. The results already obtained in this field are of such fundamental importance as to lead some to express the belief that the beginning of the end of the cancer problem is in sight. However enthusiastic such a hope may be, the most conservative estimate must acknowledge that the opportunity to study cancer under definite experimental conditions has placed the whole subject on a much firmer basis than has ever before existed.

The first definite success in the effort to transplant tumors from one lower animal to another appears to have been that of Novinsky,[1] who, in 1870, transferred a nasal cancer of a dog to two of forty-two dogs inoculated. In 1889 Wehr[2] transferred a vaginal sarcoma among dogs. Hanau's report[3] in 1889 of the transplantation of a squamous cell epithelioma of a rat by intraperitoneal inoculation, and its further transfer to a third rat, was the first to receive general credence. In 1889 Morau injected an emulsion of a cylindrical cell carcinoma of a mouse into ten other mice, and four weeks later found definite tumors of the same structure in eight of them.

During the following years he carried this tumor through seventeen generations and published the results in 1894.[4] He noted that the tumors remained stationary during gestation and that the offspring of tumor animals developed unusually large tumors.

In 1898 Velich[5] carried a sarcoma found in a rat through nine generations in rats, but he interpreted the results as a transfer of microorganisms and not as a transplantation of tumor cells. In 1901 L. Loeb demonstrated before the American Society of Pathology and Bacteriology a transplanted spindle-cell sarcoma in a rat under such conditions as to leave little doubt of its genuineness. This tumor was later transferred through about forty generations, becoming increasingly infected with bacteria. From a cystic adenocarcino-sarcoma of the thyroid in another rat Loeb[6] succeeded in growing seven generations of tumors, and Herzog[7] carried similar tumors through eight generations.

In Loeb's experiments there were several observations of importance. From the mixed tumor of the thyroid only the sarcomatous portion grew in the transplants, the carcinomatous parts being suppressed. Microscopical examination showed that the tumor grew from the peripheral cells of the transplanted piece. Tumor juice passed through filter paper proved ineffective. Pieces of tumor kept on ice five days were still viable. Tumors heated to 43 C. were markedly weakened in growth, beginning to grow later than the controls, growing more slowly and re-

gressing after five to eight weeks. Exposure to KCN, 1-700, for forty hours had the same effect as heating to 43 C. Pregnancy seemed to exert a favorable influence on the growth of the tumors. Transplanted pieces often grew more rapidly than the original tumor, but Loeb was unable to demonstrate an increase of virulence in the course of transplantation, believing that local conditions in the tumor tissue and in the inoculated animal had much to do with the rapidity of growth. Even more important was the demonstration of the value of the experimental method in the study of the general problems of tumor growth.

About this time Jensen[8] was carrying on a systematic study of a transplantable carcinoma in white mice from which reports were given during 1901 to 1903. The original tumor was a subcutaneous growth of the type of large alveolar carcinoma derived from the breast. The lymph nodes were not involved. Portions of this tumor, or its derivatives, extending over nineteen generations, were transferred to 844 mice, of which 232 died within two weeks. Of 274 mice which received subcutaneous injections of comminuted masses of the tumor 121 developed tumors, and of 238 in which a small piece of tumor was inserted beneath the skin 28 developed tumors. The tumors grew from small peripheral islands of cells which survived the transfer. Small early tumors were less effective for inoculation than older ones, and Jensen concluded that actively mitotic cells were less resistent than older quiescent ones. Gray mice were more refractory than white mice, but when once transferred to a gray mouse the resulting strain proved equally virulent for both gray and white mice. Other varieties of mice, white rats, guinea-pigs, rabbits, etc., proved immune.

The "cancer parasites" were abundant in some tumors, absent in others, and cultures for bacteria and blastomyces were negative. Complete comminution of the tumor cells or straining repeatedly through gauze removed the infectious agent from the tumor material. Kept at 37 C. for twenty-four hours, the tumor pieces lost virulence, but growth was readily obtained from pieces kept on ice for eighteen days. Exposure for five minutes to 47 C. destroyed virulence, as did drying, but the cells resisted cooling to —18 C., which Folin has shown is the critical point for the vitality of frog's muscle. The failure of about 50 per cent. of the implantations to grow, Jensen referred to slight family variations in the mice employed, but suggested that an abortive tumor might render the animal immune. He reported the cure of mouse carcinomata by means of the serum of a rabbit which had received injections of tumor cells.

Since the work of Loeb and Jensen the study of transplanted tumors in lower animals has been pursued energetically by Borrel in Paris, Ehr-

lich in Frankfort, Michaelis in Berlin, at the Gratwick Laboratory in Buffalo, by the British Commission in London, at the Rockefeller Institute, and elsewhere, and many new facts of great importance have been established.

Among these new facts may be mentioned, first, the demonstration that the inoculability of certain tumors among lower animals depends on the viability of the tumor cells, that the inoculation is a transplantation of the tumor and not an infection, since the new tumor grows from the transferred cells and not from the host's tissues. This fact has been shown for adenosarcoma of the thyroid in rats by Loeb, for the breast carcinoma in mice by Jensen, and for the lymphosarcoma of dogs by Beebe[9] and the writer. These results dispose of the supposition that the inoculability of these tumors favors the parasitic theory of their origin.

The demonstration of the extremely limited viability of tumor cells among the same or related animals is a very important result of the recent studies. Only in the mouse, rat and dog have successful transplantations been secured. The British Commission made over 900 attempts to inoculate spontaneous tumors of horses, dogs, cats and rats without a single success.[10] Ehrlich[11] reports only eleven transplantable tumors of ninety-four spontaneous growths observed in the Frankfort mice.

In rats, Hanau's epithelioma, Loeb's three growths of different structure, Michaelis' tumor, and that of Flexner and Jobling,[12] make six inoculable growths observed in this animal.

In dogs the lymphosarcoma of Wehr has been accepted by most observers as neoplasm, but with the exception of Novinsky's somewhat uncertain case, this is the sole inoculable canine tumor.

The bearing of these results on the contagiousness of human cancer is obvious. Reviewing the proportion of successful implantations in animals of the same species, it appears that success with initial transplantations is the exception rather than the rule. Among 8,000 inoculations of mice, with various mouse tumors, Bashford secured 1½ to 50 per cent. of successes. Jensen obtained, through twenty-three generations, from 20 to 40 per cent. of successful inoculations, and Borrel about 10 per cent.

With rats a considerable number of animals has always been found immune, and the same rule holds with the lymphosarcoma of dogs, Sticker[13] recording numerous failures, and Beebe finding considerable difficulty in obtaining successful inoculations from primary growths.

It soon was apparent that tumors become increasingly virulent when repeatedly passed through mice of the same breed. The Jensen tumor, yielding 40 per cent. of successful inoculations in white Danish mice,

was sent to London, Berlin, Paris and Buffalo. Workers in each of these localities had some difficulty in keeping the strains alive, but by repeated inoculations successful results rapidly increased. Marked differences in susceptibility have been observed in the same locality between gray and white mice and between wild and tame mice of the same color. In fact, Haaland[14] has shown that Ehrlich's highly virulent sarcoma is virulent only for Berlin mice, but not for Danish mice, and that inbred animals are more susceptible to a tumor from the parents than are cross-bred animals. When the Berlin mice were housed and bred in Christiania they shortly became refractory to the Berlin (Ehrlich's) tumor. This remarkable transformation Haaland cautiously refers to change of diet. In Berlin the mice were fed chiefly on fat and animal proteid (milk), in Norway on carbohydrates.

These observations show that mouse tumor cells are adjusted with extreme delicacy to the nutrient soil, and that their growth or regression is determined by factors far more subtle than any heretofore demonstrated in immunity relations.

The study of transplanted tumors promises to throw light on some obscure phases of histogenesis in tumors. Loeb[8] observed that a diffuse spindle-cell sarcoma of a rat, when transplanted, assumed types of cellular arrangement designated as perithelioma (atypical), alveolar sarcoma or endothelioma, myxoma, and diffuse spindle-cell sarcoma. In a rat with a mixed adenocarcino-sarcoma of the thyroid he found, in the lung, a pure sarcomatous metastasis, and on transplanting a portion of mixed tumor observed only the sarcomatous elements in the secondary growth. The significance of this latter observation was elucidated more fully by Ehrlich,[11] who in the tenth generation of a carcinoma encountered a mixed sarcoma and carcinoma which by the thirteenth and fourteenth generations became a pure large spindle-cell sarcoma without carcinomatous elements, maintaining this character for at least fifty generations.

With another strain a similar transformation was observed, while a permanent mixed tumor was produced from the mixed material obtained from four strains, all of which were originally pure carcinoma. Apolant[15] and later Bashford[16] claim to have traced the development of the sarcoma from the stroma cells, although admitting the existence of cells which suggest a transformation of cancer into sarcoma cells.

Among human tumors the transformation of carcinoma into sarcoma is unknown. Metastatic melanoma of epithelial origin may, however, assume the characters of pure spindle-cell sarcoma. In adamantinoma the masses of enameloblasts which compose the tumor form areas of large

spindle cells whose epithelial nature is proven by their formation of abortive enamel. In human tumors, therefore, the presence of spindle cells is not a sufficient indication that one is dealing with sarcoma, and further information about the spindle cells of mouse cancer is required before the exact significance of the transformation of carcinoma into sarcoma can be determined. In transplanted mouse tumors, such spindle cells may be derived from (1) epithelium, (2) from the sarcomatous portion of a mixed tumor, (3) from the transplanted stroma, or (4) from the connective tissue of the host.

Working with mixed material of sarcoma and carcinoma it has been found possible to suppress, artificially, either element, since Haaland found Berlin mice susceptible only to the sarcoma, Danish mice only to the carcinoma, and Bashford believes he has hastened the transformation into sarcoma by immunization against the epithelial element.

The distinctions between benign expansive and malignant infiltrating growth are not rigidly maintained in experimental tumors of mice. The rate of growth of Jensen's cancer shows cyclic variations extending over periods of about 200 days (Bashford[17]). At the period of greatest growth it develops expansively and produces metastases without infiltrating tissues. Intraperitoneal implantation and advanced metastases of the same tumor, however, infiltrate neighboring organs, but when the infiltrating tumor is replanted subcutaneously the growth is again expansive. These distinctions, so important for the host, are, therefore, more or less accidental for the tumor. The occurrence of spontaneous variations in structure of the same tumor, transplanted in susceptible animals, may be kept in mind in considering Apolant's report[18] that by transplanting solid carcinoma in actively immunized mice he was able, in three instances, to transform the carcinoma into a benign adenoma.

In the transplanted tumor graft the specific cells multiply, but the stroma perishes and a new stroma is provided by the host's tissues. A possible exception to the rule is found in the transformation of carcinoma into sarcoma, reported by Ehrlich and Bashford, which they interpret as a neoplastic process becoming established in the host's connective tissues. In the lymphosarcoma of dogs we[9] have described the appropriation of some of the small transplanted blood vessels by the new growing tumor. In metastases of mouse carcinoma the invaded tissues supply stroma, but are, as a rule, otherwise passive. Haaland, however, described the transformation of pulmonary epithelium into tumor cells in metastases of mouse carcinoma.

This interpretation of Haaland has not been confirmed and will doubtless meet with energetic opposition. Such a process is not recog-

nized in human tumors, but, notwithstanding the determined position of Ribbert and Borrmann,[20] based chiefly on the study of gastric cancer and superficial epitheliomata, many (Virchow,[21] Hauser[22]) believe that there may be a gradual extension of the originating focus of a tumor. In primary adenocarcinoma of the intestine, and in melanoma, I believe that there may be a gradual transformation of normal epithelium into tumor cells.

Ribbert[23] has lately modified his former rigid position on this important question by admitting that cancers may arise from several foci, some of which appear later than others, and that there may be a gradual fusion of the tumors growing from these foci. It is obvious, however, that the distinction between primary tumors arising successively from adjoining foci and the gradual extension of a tumor process through normal cells is a matter of two interpretations of the same appearances.

Immunity.—Evidences of a peculiar type of immunity have from the first appeared in the observations on experimental tumors. Wehr[2] in 1883 described the spontaneous regression of the lymphosarcoma of dogs, a fact repeatedly verified for the same tumor by Sticker and Beebe. Loeb noted the complete absorption of many of his transplanted sarcomas in rats. Gaylord and Clowes[24] reported 20 per cent. of spontaneous cures of the Jensen mouse tumor, and they first drew attention to the significance of this fact as an indication of acquired immunity. The exact meaning is, however, obscured by the fact that some tumors regress while others grow in the same animal, and some after regressing for a time recover and go on to a fatal termination. A slight deterioration in the general health of the animal may interrupt the regression.

That local factors play a part in the limitation of the growths is indicated by the histologic study of regressing tumors. Such tumors are usually surrounded by a connective tissue capsule which invades the cellular edges, blocks the blood vessels, which are often sheathed with round cells, and cuts off the nutrition. In regressing dog tumors we find fatty degeneration, transformation of large lymphocytes into small, compression atrophy at the periphery, and foci of liquefaction necrosis in the center, mingled with areas of actively multiplying cells. If no other factor than anemia were present these would be the logical changes. Loeb[6] found that if a regressing tumor were subdivided and replanted in the same animal it would often begin to grow rapidly. This observation is not in accord with the view that specific immune substances are present in the blood of animals recovering from tumors.

In July, 1905, Gaylord and Clowes[24] reported that thirty mice which had spontaneously recovered from definite tumors had proven immune

to further inoculation with the same tumor, and that ten had resisted a third inoculation with a more virulent tumor. There were thus indicated: (1) The existence of acquired immunity against mouse cancer, (2) the possibility of increasing this immunity by a process of vaccination. In later experiments they were able to reduce the proportion of successful implantations of the Jensen tumor from 30 to 50 per cent. in the first series, to 10 per cent. for the second series, and to complete immunity in all surviving animals to the third inoculation. Yet, by vaccination with the Jensen tumor, they could not fully protect against the highly malignant Brooklyn cancer. Ehrlich,[25] by employing a hemorrhagic tumor which produced small abortive growths or none, was able to protect against tumors of maximum virulence. By repeatedly inoculating either the mouse sarcoma or the carcinoma he was able to protect against both sarcoma and carcinoma, and to a less extent against a chondroma, whence he concluded that the resistance established constituted a sort of pan-immunity against tumors. Bashford also obtained a high proportion of immune mice after spontaneous cure of tumors, and to a less extent after a negative inoculation of cancer tissue, which was promptly absorbed.

On the other hand, Haaland,[14] by inoculation of Jensen's tumor, could not immunize Berlin mice against Ehrlich's very virulent sarcoma, and Michaelis[27] could not immunize white mice by means of cancers from gray mice, nor Berlin mice by tumors from animals bred in Copenhagen. It is possible that differences in technic and in the tumors employed may explain these conflicting results. At any rate, the large number of observations recorded show that a certain type of resistance against cancer has been produced in mice.

That a true specific immunity against tumors has been demonstrated beyond question can not at present be claimed, for there are many disturbing factors which must be considered in the interpretation of the results of vaccination. The methods employed involve a process of elimination of weaker animals, which succumb to the treatment, and some of the animals which appear to have been rendered immune by the vaccination may always have been naturally immune to all the tumors employed, and this source of error can hardly be eliminated from statistical studies in which the condition of individual animals is not fully determined. Or non-specific variations in the general health of the animals may determine the result in mice, as it often does in dogs, and this factor can not be estimated accurately in such small animals as mice.

Again, Bashford[17] has shown that different portions of the same tumor, and the same tumor at different periods of growth, vary in rate

of growth, and that highly virulent strains may suddenly decline in virulence, but most of the experiments in immunization depend for validity on the assumption of uniform virulence of the tumor strains. Much depends on the dosage employed to test immunity. Successful results may follow multiple inoculations when a single implantation is negative, and Michaelis has seen a mouse, inoculated three times without result, take the fourth inoculation.

Finally, the artificial resistance against tumors does not appear to be specific. The pan-immunity observed by Ehrlich is a suspicious feature, suggesting the action of unknown and complex factors. Michaelis,[27] by the injection of normal mouse liver, was able to secure considerable immunity against tumors. Schöne,[28] with the liver of mouse embryos and normal mice; Borrel and Bridré,[29] with liver or spleen, and Bashford,[30] with mouse red cells, all succeeded in rendering mice quite refractory to the growth of cancer cells. Bashford found that mice convalescent from infectious diseases were refractory to tumor cells, and he and Tyzzer[31] record the very interesting observation of the spontaneous development of cancer in mice which resisted inoculation. Lately[30] he reports that of all embryonal organs, inoculation by epithelial tissue gives the highest degree of immunity against cancer. Pregnancy retards the growth of mouse tumors and renders the animal less susceptible to inoculation. Reference may again be made to the remarkable results of increase in resistance observed by Haaland in Berlin mice transferred to Christiania, and probably due to change of diet, water and climate.

All of these considerations show that resistance of mice to tumors is of exceedingly complex nature and probably not comparable to any known form of immunity.

Not only may mice be made resistant to tumors, but their natural resistance may be diminished. In dogs there is a close relation between the general health of the animal and their susceptibility to inoculation with, and the rapidity of growth of lymphosarcoma, while inoculation with the filtered products of this tumor increases their susceptibility. Clowes[26] and Baeslack found that mouse tumors heated to 42 C. were more readily inoculable. This result is probably due to the greater proportion of autolytic products in the heated material. This same explanation probably applies to the results of Flexner and Jobling,[32] who rendered rats more susceptible to their tumor by injections of heated tumor products. They made the additional observation that the animals were especially susceptible, not immediately, but from the tenth to the thirteenth days after receiving the tumor products, suggesting a form of

anaphylaxis. In the same line Borrel[33] suggests that perhaps mice may be made more susceptible to cancer by a diet of cancer tissue. It is known that the repeated injection of toxic proteids, both of bacteria and of organ cells, produces not immunity but increased susceptibility, and there seems to be no reason why this susceptibility may not have the characters of anaphylaxis, but that it does has not yet been proven.

The effort to determine the nature of the immune forces against cancer has led to the formation of theories which have required frequent readjustment. It was natural to suppose that the blood serum of immune animals must contain substances directly antagonistic to tumor cells. This belief led Gaylord, Clowes and Baeslack[34] to inject tumor mice with the serum of recovered animals. Their first results were highly encouraging, since a minute quantity, 2 c.c., seemed to cause the rapid disappearance of some large tumors, while normal serum was entirely ineffective. These results, however, were not constant. They then mixed tumor emulsion with immune serum before injection, using salt solution and normal serum as controls, and found that the immune serum mixture gave 12 per cent. of successful inoculations, as compared with 31 per cent. for the controls. These results also are of uncertain value on account of many disturbing factors, but they indicate a cytotoxic action of the immune serum.

It first appeared that the active growth of a tumor was necessary to confer immunity, but Bashford[30] concluded that while the resistance established by a growing tumor is greater than that following an abortive inoculation, there is no relation between the grade of resistance established and the energy of growth or virulence of the tumor inoculated, but the protection is proportional to the quantity of tumor absorbed. In this case immunity must, apparently, depend on antagonistic substances produced in the body against tumor proteids. Yet, in the serum of actively-immunized mice, Michaelis[27] failed to find any evidence of cytolytic or agglutinative action on the tumor cells, or of complement fixation by the Bordet-Gengou method. Tumor cells treated with immune serum, with normal rabbit serum, with rabbit serum rendered hemolytic to mouse red cells, and with serum of animals receiving injections of killed mouse tumor, grew quite as well as the controls. Borrel[33] failed to find any immunizing or curative influence in the serum of a sheep receiving thirteen injections of 100 gm. each of mouse cancer. As yet there has been no satisfactory evidence of the existence in the serum of immune animals of substances directly antagonistic to tumor cells.

Beebe and Crile,[35] after exsanguinating dogs suffering from advanced lymphosarcoma, have directly transfused them with large quantities of

the blood of naturally immune or recovered animals. The result in nine cases was a rapid and complete disappearance of the tumors. This bold experiment would seem fully calculated to demonstrate in immune blood the presence of substances antagonistic to these tumor cells. Yet it is quite legitimate to suppose that the transferred immune blood was a more suitable nutriment for the body cells, and that as a result of the transfusion the balance of nutrition was reversed, the metabolism of the healthy tissues was improved, while that of the tumor was relatively depressed by the withdrawal of nutriment to such an extent that it underwent simple atrophy.

Athrepsia.—The observations on the viability of tumor cells in related animals has, from the first, suggested that the growth or regression of a tumor is determined by very slight variations in the soil, and that the problem of immunity is here one of the nutrition of the tumor cells. Ehrlich is the legitimate spokesman in this field, and he has designated[11, 36] this form of immunity as "athreptic." Transplanting mouse carcinoma into rats, he observed that the plant grew for several days, as in the mouse, but thereafter regressed. If, after a sojourn in the rat, the piece was transferred back to the mouse, it grew with undiminished vigor, after which it was again susceptible of considerable growth in another rat, but not in the one first receiving it. This zigzag transplantation he maintained for several generations. From these observations he concluded that the mouse tumor carried over into the rat a specific substance, or "X-stoff," which enabled the tumor cells, for a time, to absorb nutriment from the rat, but on the consumption of which the tumor ceased to grow and required a renewal of the specific substance in the mouse. Since a rat once serving as temporary host for the mouse tumor became thereafter entirely refractory to the growth and could not serve a second time, it appeared that the tumor must soon absorb the limited supply of suitable nutriment in the rat or else that the rat once inoculated developed antibodies against the mouse cells.

Two forms of athreptic immunity are, therefore, possible. In one the specific substance is not itself the nutrient molecule, but merely facilitates absorption, although it is slowly consumed in the process. This theory finds an analogy in the relation of corpus luteum secretion to the chorionic epithelium. In the other view the specific substance is the nutrient molecule and is consumed in the growth. To what extent these hypotheses will prove adequate to explain immunity in tumors it remains for the future to decide.

That mouse tumors transplanted into rats fail to grow is doubtless due, to some extent, to the unfavorable soil. Here the influence of

athrepsia seems obvious. But the fate of mouse tumor in rats recalls the experiment of Cohnheim and Maas,[37] who injected into the jugular vein of rabbits fragments of periosteum and saw them develop in the lung into islands of bone which grew for two or three weeks, but thereafter were absorbed. There is good reason to believe that these same islands of bone replaced beneath the periosteum would have retained their vitality. Here the influence of athrepsia is not so obvious, but other factors concerned in tissue organization seem to be at work.

It seems to be a fact also that tumors often regress in inoculated animals in which the soil is fully capable of supporting the growth, as is shown by successful reinoculation, but in which other factors, some of them local, interfere with the growth and effect a cure. A study of the conditions under which tumors naturally develop and grow indicates that suitable soil is of vastly wider distribution than is the occurrence of tumors, and that the fate of man or animal suffering from a malignant tumor depends chiefly on the characters of the cells and not on the soil. Outside of the experimental laboratory the soil seems to bear much the same relation to appropriate tumor cells as it does to the tubercle bacillus.

It might be supposed that tumor cells grow, not because they possess increased avidity for nutriment, but because the general body cells are deficient in this function. Yet tumor cells grow rapidly in young animals which show no such constitutional basis for the growth of tumors.

Chemistry of Tumors.—The chemical study of tumors forms a necessary preliminary to the construction of theories of immunity. If chemical or biochemical distinctions can be found between tumor cells and other tissues, then, and not till then, can a chemical or biochemical theory of immunity be established. Several interesting lines of research have extended into this field.

In rapidly-growing tumors, free from necrosis, Beebe[38] found an excess of potassium and a deficiency of calcium, while opposite conditions held in old and necrotic tumors. Clowes[39] observed the same relations in mouse tumors.

The proteids of tumors are said to differ in construction from those of normal tissues. On analysis, by Wolf,[40] cancer tissues yielded a high proportion (35 per cent.) of glutaminic acid, while alanin, phenylalanin, asparaginic acid and diaminoacids were increased, and leucin diminished, in the results of Bergell and Dorpinghaus.[41] These results conflict with those of Petry,[42] Neuberg[43] and Beebe.[44]

Nucleo-histon is present only in lymph nodes among normal tissues, and its appearance in cancers secondary in lymph nodes suggests that

metastatic tumors receive a chemical impress from the tissue in which they are growing (Beebe[44]).

Cellular tumors often appear to undergo autolysis more rapidly than many normal tissues, but it is doubtful if there is any normal tissue with which a comparison may properly be made. Petry[42] observed that antiseptic autodigestion of a breast cancer proceeded more rapidly, but in the same manner as that of a normal breast tissue. Yet he is extensively quoted as having proven that tumors, in general, autolyze more rapidly than normal tissues. Comparing the increase in non-coagulable nitrogen in a carcinoma of the liver with that of the remaining liver tissue, during autolysis, Beebe[53] noted a considerable excess in favor of the tumor.

It is well known that tumors are very subject to softening and necrosis from infection and imperfect blood supply, but I do not think it has yet been proven that well nourished tumor tissue undergoes autolysis more rapidly than an equivalent normal tissue. Beebe and the writer[45] passed dog blood by artificial circulation through test tubes containing fragments of dog sarcoma. Under these conditions the sarcoma cells remained alive for eight or ten days, but dog liver and kidney cells became necrotic and autolyzed extensively in forty-eight hours.

The study of special ferments in tumors was introduced by Buxton,[46] who, with Shaffer,[47] found no distinct differences in quantity or quality from those of normal organs. Harden and McFadyen[48] found in tumors proteolytic ferments acting in acid and alkaline media, respectively, thus disproving Beard's supposition that proteolysis of tumor ferments is exclusively acid. A strongly hemolytic activity of extracts of degenerating, and especially of necrosing tumors, has been demonstrated by Weil[49] as a factor in tumor cachexia, but this action is not specific.

Petry[50] found that the injections of extracts of fresh or of autolyzed cancers failed to disturb the nitrogen elimination in dogs, and he doubted if any of the cancer extracts were really active in the living body.

Blumenthal and Wolf[51] submitted five cancers to acid peptic and alkaline tryptic digestion. Two of them resisted pepsin, but three were digested readily in it, while all five were readily digested by trypsin. Yet they state that resistance to peptic and susceptibility to tryptic digestion is characteristic of cancer. Their results probably depended on a high proportion of nucleo-proteids in some of the tumors and not on any significant peculiarity of tumor proteids. In two trials emulsion of cancer tissue not only dissolved itself but hastened the autolysis of liver pulp, whence they conclude that tumor ferments are not merely autolytic, as are those of normal tissues, but heterolytic. From these

observations, which Neuberg[52] endorses, Blumenthal does not hesitate to draw far-reaching conclusions regarding the action of ferments in tumors, claiming that their infiltrative growth and the cachexia which they produce are dependent entirely on the above characters of their ferments. The possible presence of bacteria, accidental necroses and postmortem decomposition in the tumors examined is not mentioned by these writers, and until their observations are reasonably controlled and greatly extended their conclusions can not be trusted.

There are chemical problems in tumors, but the problem of tumors is not chemical. An experiment in antiseptic autolysis of comminuted cells, prolonged over several months, may be sound for chemistry, but is it fruitful for pathology? In these and other experiments the language employed and the conditions secured are those of chemistry, but the conclusions are drawn in a physiologic sense. Yet between the two there is a wide gap of assumption. The help of the chemists is needed, but until their technic approaches more closely to physiologic requirement it would seem that some of their results need not detain us long. The present studies do not, as a whole, offer a satisfactory demonstration that tumor cells possess chemical peculiarities sufficient to justify the assumption that they represent a specific biologic series.

In a biochemical sense the efforts to demonstrate specific qualities in tumor cells have not been fully successful. Mention has been made of Michaelis' failure to produce cytolytic, agglutinating, or precipitating agents specific for mouse tumor cells. Working with purified nucleoproteids, Beebe[53] has been somewhat more successful. From the nucleoproteids of a leukemic spleen he produced a serum which agglutinated the emulsified cells of this spleen and also those of a lymphosarcoma, and precipitated the nucleoproteids from these sources, but acted very feebly and only in strong concentration on cells and nucleoproteids from normal spleen and other tissues, as well as from cancer and spindle-cell sarcoma. Similar results were obtained from the nucleoproteids of cancer. If these indications prove trustworthy, then a biochemical basis for immunity against tumors may be within reach.

If any general criticism of the recent trend of cancer research is to be made it must apply to the exclusive relation of these studies to the nature of the established tumor process and their failure to deal with the origin of tumors. These problems seem to be entirely distant. Tumors grow readily in young dogs, rats and mice, although these young animals seldom or never develop such tumors spontaneously.

From this standpoint the more fundamental character and permanent value of the long line of studies on cell autonomy become conspicuous.

for these deal with the origin of tumors. No one has yet succeeded in originating a malignant tumor experimentally, although the occasional effects of the *x*-ray may be so regarded. Very broad theoretic deductions have been drawn in the elaborate study by von Dungern and Werner[54] regarding the response of epithelial cells to various stimuli. Fischer[55] has shown that extensive epithelial hyperplasia may be induced in the rabbit's ear by forcible injection of oil containing Sudan III, which seems to exert a peculiar attraction for certain epithelial cells of the skin. These observations may later be of value in the experimental production of tumors, but the essential character if a neoplasm, progressive growth, is so far lacking in the process excited by this method in the hands of many experimenters.[56] The long history of efforts to produce tumors experimentally indicates that many have been in control of single factors in tumor genesis, but no one has combined enough of these factors to secure the concrete result of a growing malignant neoplasm.

I am strongly of the opinion that information of fundamental importance in this field is still to be obtained by the very minute observation and analysis of the general and local conditions surrounding the early stages of cancer. This is the exclusive opportunity of the clinician, medical, surgical, and special, but it is often neglected. In it lies the chief hope, for the present generation, of a reduction in the mortality from cancer, by the earlier recognition of the precancerous stage of the disease and the elimination of some of its accessible factors.

The new era has not succeeded in devising a cure for cancer. While some are very confident, there does not seem to be legitimate ground for hope that any will shortly be discovered. The chief definite limitation of the knife has come from a most unexpected quarter, in the form of the *x*-ray, which affects favorably only superficial tumors of moderate malignancy. Standardized *B. prodigiosus* toxins, as now used by Coley, are applicable only to a limited group of sarcomata. The *x*-ray, bacterial toxins, vaccination with *micrococcus neoformans,* inoculation with the substance of thyroid, thymus, liver, and other toxic proteids, serum prepared against cancer tissue or its proteids, and Beard's pancreatin, all produce more or less destruction of the older portions of true cancers, with deceptive reduction in the size of the tumor, while the patient goes on to die from progressive infiltration by the more resistant tumor cells, and with accelerated metastases and cachexia.

The recent studies of artificial immunity to tumors in lower animals touch closely on the problem of the control of tumor growth in man, but the highly artificial conditions which form the basis of these experi-

mental studies may cause disappointment when the attempt is made to transfer to man the results secured in lower animals. Yet the situation is encouraging in the present fixed determination to acquire more facts, in which field the experimental method is truly epoch-making, and cancer research may justly be stimulated, now more than ever before, by the reflection that a vast practical importance may at any moment attach to the new facts that are being gathered.

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A CONTRIBUTION TO OUR KNOWLEDGE OF THE ACETONE BODIES.

WITH A CLINICAL METHOD FOR THE QUANTITATIVE ESTIMATION OF DIACETIC ACID AND ACETONE.*

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The scientific and clinical importance of acetone bodies, viz.: acetone, diacetic and oxybutyric acids, is demonstrated by the many investigations which have been made regarding them in the last decade. As evidences of disordered metabolism they are of significant value. The Germans have been the leaders in this promising field of research, but many valuable studies have come from our own countrymen, among which may be recalled the work of Herter, Joslin, Brewer, Baldwin, Hubbard, Brackett, Stone, Low and others.

While much of the earlier work led to conclusions more or less contradictory, the more recent observations permit us to coordinate our knowledge and are full of promise for a rational system of prophylaxis and therapy. It seems worth while, therefore, to review some of the facts as we know them to-day.

THE RELATION OF THE ACETONE BODIES TO ONE ANOTHER.

The relationship of the acetone bodies is a result of their chemical constitution and is made evident by examining their graphic formulæ.

B-oxybutyric acid.	*Aceto-acetic acid.* (*Diacetic acid.*)	*Acetone.*
CH_3	CH_3	CH_3
|	|	|
CHOH	CO	CO
|	|	|
CH_2	CH_2	CH_3
|	|	
COOH	COOH	

By oxidizing oxybutyric acid we obtain diacetic acid, and when

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diacetic acid is heated to 100 degrees C. it is readily decomposed into acetone and carbonic acid. The latter reaction occurs so readily that hitherto no satisfactory method has been devised of separating the acetone and diacetic acid of the urine and, therefore, all quantitative estimations of acetone represent the combined output of diacetic acid and acetone.[1] By a laborious process we are able, however, to estimate separately the amount of oxybutyric acid.

TABLE I.—Showing Appearance of Diacetic Acid When Acetone Is Excreted in Considerable Quantities.

Case.	Date.	Diagnosis.	Acetone Tests.		Diacetic Acid Tests.				Amount of Acetone in 24 hours in grams.	Rotation.	
			Lieben's.	Legal's.	Arnold's.	Gerhardt's.	Diazo.	Riegler's.		Before Fermentation.	After Fermentation. Indicating Presence of Oxybutyric Acid.
C. C. K. .	5, 25, '05	Diabetes. . .	+	0	0	0	. .	. .	0.018		
M. E. M. .	5, 9, '05	Diabetes. .	+	0	0	0	. .	0	0.017		
L. H. . . .	6, 7, '05	Diabetes. .	+	?	0	0	. .	. .	0.021*		
B. B. . . .	6, 25, '05	Diabetes. .	+	+	0	0	. .	. .	0.037*		
C. C. K. . .	6, 27, '05	Diabetes. .	+	+	0	. .	. .	. .	0.060		
L. B. . . .	5, 10, '05	Diabetes. .	+	+	+	0	0	0	0.068		
C. C. K. .	6, 13, '05	Diabetes. .	+	+	+	0	0	0	0.399		
F. J. M. . .	6, 8, '05	Diabetes. .	+	+	+	0	0	. .	0.160*		
G. L. . . .	5, 1, '05	Diabetes. .	+	+	+	+	+	. .	0.800		
S. C. . . .	5, 5, '05	Diabetes. .	+	+	+	+	+	. .	0.616		
G. L. . . .	5, 15, '05	Diabetes. .	+	+	+	+	+	?	0.657		
G. L. . . .	6, 5, '05	Diabetes. .	+	+	+	+	+	?	1.113		
S. B. C. .	5, 3, '05	Diabetes. .	+	+	+	+	+	. .	1.111*		
G. L. . .	5, 8, '05	Diabetes. .	+	+	+	+	+	+	1.333*	+0.5	—1.2
J. F. . . .	2, 12, '04	Diabetes. .	+	+	+	+	+	. .	0.262	+6.0	—1.0
J. F. . . .	2, 22, '04	Diabetes. .	+	+	+	+	. .	. .	0.962	+6.8	—0.4

NOTE. +, positive reaction; ?, doubtful reaction; 0, negative reaction; *, amount in one litre.

It seems to be established that oxybutyric acid is the antecedent body from which diacetic acid and acetone are formed. Schwartz[2] has given diacetic acid by mouth to diabetic animals and has seen a partial conversion into acetone in the urine. Geelmuyden[3] gave sodium salts of diacetic acid to normal men who were on a mixed diet and a diet without carbo-

TABLE 2.—Conditions Under Which the Acetone Bodies Are Excreted.

Condition or Disease.	Acetone.	Diacetic Acid.	Maximum Amount of Acetone in 24 hours in grams. Estimations Include Diacetic Acid.		Oxybutyric.	Amount of Oxybutyric Acid in 24 Hours in Grams.	Observer.
			Urine.	Breath.			
Normal	+	..	0.010	.....	..	.....	v. Jasch.
Normal	+	..	0.015	.....	..	.....	Boeri.
Normal	+	..	0.018	.....	..	.....	v. Engel.
Normal	+	..	.....	0.023	..	.....	Müller
Starvation	+	..	0.703	.....	..	.....	Hirschfeld
Starvation	+	..	0.784	.....	..	.....	Müller.
Starvation	+	+	.....	.....	+	2.98	Waldvogel.
Starvation	+	+	0.699	.....	+	1.60	Waldvogel.
Starvation	+	..	0.431	0.469	..	.....	Joslin.
Starvation and oleic acid	+	..	0.926	0.847	..	.....	Joslin.
Digestive disturbances	+	+	.....	.....	+	.....	Lorenz.
Digestive disturbances	+	+	.....	.....	+	....	Magnus-Levy.
Diarrhea	+	+	4.000	.....	..	.....	Beauvy.
Auto-intoxication	+	+	0.500	.....	..	.....	Beauvy.
Appendicitis	+	+	0.400	.....	..	.....	Beauvy.
Typhoid fever	+	+	1.000	.....	..	.....	Beauvy.
Typhoid fever	..	..	.....	.....	+	.....	v. Noorden.
Erysipelas	+	+	0.800	.....	..	.....	Beauvy.
Variola	+	+	0.500	.....	..	.....	Beauvy.
aricella	+	+	0.600	.....	..	....	Beauvy.
Measles	+	+	0.800	.....	..	.....	Beauvy.
Measles	..	..	.....	.....	+	.....	Kulz.
Scarlatina	+	+	0.700	.....	..	.....	Beauvy.
itis	+	+	0.500	.....	+	.....	Beauvy.
Diphtheria	+	+	0.700	.....	..	.....	Beauvy.
Pneumonia	+	+	1.000	.....	..	....	Beauvy.
Tubercular meningitis	+	+	0.600	.....	..	.....	Beauvy.
nesthesia	+	+	.....	.....	+	.....	Waldvogel.
Diabetes mellitus	+	+	10.+	.....	..	.....	Naunyn.
Diabetes mellitus	+	+	19.000	.....	..	....	Magnus-Levy.
Diabetes mellitus	+	+	4.200	3.600	..	.....	Schwartz.
Diabetes mellitus (mixed diet)	+	+	.....	.....	+	12.1	Wolpe.
Diabetic coma	+	+	.....	.....	+	22.8	Wolpe
Diabetic coma	+	+	.....	.....	+	16.0	Minkowski.
Diabetic coma	+	+	.....	.....	+	188.0	Naunyn.
Diabetic coma	+	+	.....	.....	+	100 to 150	Magnus-Levy.

hydrates, and found an increase in the acetone output in each instance. Minkowski[4] gave a dog with pancreatic diabetes 10 grams of sodium oxybutyric acid, obtaining as a result a large amount of diacetic acid and acetone in the urine.

The relationship of the acetone bodies is also evident when we consider the order in which they make their appearance in the urine. For example, in a progressive case of diabetes mellitus, the first of these bodies which we find is acetone. As the process advances we next detect diacetic acid, and when diacetic acid has increased to a considerable amount oxybutyric acid appears. When a bad case of diabetes begins to improve, the acetone bodies disappear in the inverse order in which they occurred; oxybutyric acid is the first to go, followed by diacetic acid and finally by acetone. These sequences, ascending and descending, indicate respectively the progressive failure and improvement of oxidation. I think we may look on the excretion of oxybutyric acid and diacetic acid as invariably due to pathologic conditions, and the appearance of any considerable amount of acetone must be regarded in the same light.

CONDITIONS IN WHICH ACETONE BODIES OCCUR.

Recent observation has demonstrated that the excretion of the acetone bodies occurs in a wide number of diseases and under many conditions. Acetone may be excreted in the urine in very small amounts in health under normal conditions. v. Engel[5] puts the normal limits at from 0.006 to 0.018 gram of acetone in 24 hours. In pathologic conditions, acetone is thrown off in the expired air as well as in the urine, but diacetic and oxybutyric acids can not escape by way of the lungs and are excreted by the kidneys alone. There seems to be no constant ratio between the amount of acetone excreted by the kidneys and by the lungs. Schwartz,[6] in some of his determinations, found 70 per cent. of the acetone in the expired breath. The acetone bodies are excreted in considerable quantity in starvation; in certain digestive disturbances; in many febrile diseases, such as the exanthemata, pneumonia and typhoid fever; after surgical operations; during pregnancy and labor; after the administration of certain drugs, among which are benzol, antipyrin and morphin; following poisoning with phosphorus, phloridzin, atropin, coal gas, curare and lead. In diabetes their amount may be very large. Naunyn[7] reports a case in which there was an output of 188 grams of sodium oxybutyric acid in a single day.

Table 2 will indicate the various conditions under which acetone bodies are excreted, with the maximum amounts as noted by numerous observers.

IMPORTANCE AND PRACTICAL VALUE OF ESTIMATING THE ACETONE BODIES.

If acetone bodies are excreted in any considerable quantity, it is positive evidence of improper metabolism. Their study is not only of value because it furnishes us with knowledge important in making a correct diagnosis and prognosis, but also because it affords us a means of following our patient's condition from day to day and of estimating the value of the therapeutic measures which we are using.

In following a case of diabetes mellitus, observations on the acetone body excretion are as important as a knowledge of the sugar output. As soon as diacetic acid appears in the urine, however small may be the amount of glucose excreted, we should recognize that an improper metabolism of fat is in progress. The appearance of oxybutyric acid indicates that the body cells are burning their fuel even less well, that a condition of acid intoxication is imminent, and that coma, however remote, may threaten at any moment.

Recent observations on acid intoxication during confinement and following surgical operations makes their estimation of importance in these conditions. Such studies should be useful in estimating the value of the dietary of large institutions. Here the alienist may find evidence of starvation in cases in which it is suspected but unproved. Knowledge of the progress of acetone body excretion is of value in all chronic diseases with tissue destruction and in acute disease with rapid wasting.

I think that from what has been pointed out it will be conceded that the estimation of the acetone bodies is important and of wider application than is usually supposed.

A CLINICAL METHOD OF ESTIMATING THE ACETONE BODIES.

For the purpose of following the acetone body excretion at short intervals in general practice the usual quantitative methods are too laborious. Furthermore, as it has already been pointed out in many cases, a very large part of the acetone is excreted by the lungs, the determination of the acetone of the breath is an undertaking impossible in general practice, but, unless this is estimated, the exact quantitative determination of the amount of acetone in the urine is in itself of little value. If, however, we could estimate the acetone bodies excreted by the kidneys by means of a short, simple method, which requires little time and is approximately accurate, it would afford us knowledge of great value in following quantitatively the changes from day to day. The need of such a method has induced the present study and has led me to devise a simple clinical method based on the delicacy of the well-known test-tube reaction in urine containing the acetone bodies.

TABLE 3.

Name.	Date.	Acetone.		Diacetic Acid.		Oxybutyric Acid.	Acetone, grms per liter.	
		Lieben's.	Legal's.	Arnold's.	Gerhardt's.			
C. C. K. .	5, 25, '05	+	0	0	0	. . .	0.014	Lieben's positive, Legal's negative. Acetone = less than 0.030 grms. to 1 liter.
M. E. M. .	5, 9, '05	+	0	0	0	. . .	0.015	
E. R. W. .	3, 26, '06	+	0	0	0	. . .	0.019	
N. R. . . .	9, 24, '05	+	0	0	0	. . .	0.029	
L. H. . . .	6, 7, '05	+	?	0	0	. . .	0.021	Lieben's and Legal's positive, Arnold's negative. Acetone = 0.030 to 0.100 grms. to 1 litre.
E. R. W.. .	3, 12, '06	+	+	0	0	. . .	0.031	
St. M . . .	1, 5, '06	+	+	0	0	. . .	0.031	
E. R. W.. .	1, 29, '06	+	+	0	0	. . .	0.040	
C. C. K. . .	4, 27, '05	+	+	0	0	. . .	0.039	
B. B. . .	4, 25, '05	+	+	0	0	. . .	0.037	
E. S. . . .	11, 29, '05	+	+	0	0	. . .	0.080	Arnold's positive, Gerhardt's negative. Acetone = 0.100 to 0.200 grms. to 1 liter.
E. R. W....	3, 2, '06	+	+	+	0	. . .	0.100	
C. C. K. .	6, 13, '05	+	+	+	0	. . .	0.155	
F. J. M. .	6, 8, '05	+	+	+	0	. . .	0.160	
C. C. K. .	12, 18, '05	+	+	+	+	. . .	0.214	Lieben's, Legal's, Arnold's and Gerhardt's all positive. Acetone = more than 0.200 grms. to 1 liter.
C. C. K. .	1, 13, '06	+	+	+	+	+	0.331	
G. H. M.. .	6, 16, '06	+	+	+	+	. . .	0.340	
G. L. . . .	4, 1, '05	+	+	+	+	. . .	0.500	
A. B. . . .	1, 29, '06	+	+	+	+	. .	0.640	
G. L. . . .	5, 1, '06	+	+	+	+	. . .	0.700	
G. L. . . .	3, 19, '06	+	+	+	+	. . .	0.800	
N. R. . . .	12, 7, '05	+	+	+	+	. . .	0.888	
S. B. C. . .	5, 3, '05	+	+	+	+	. . .	1.111	
G. L. . . .	5, 8, '05	+	+	+	+	+	1.333	
G. L. . . .	1, 8, '06	+	+	+	+	+	3.200	
J. F. M .	1, 3, '06	+	+	+	+	+	4.000	

The following conclusions are based on the examination of over 600 specimens of urine for the acetone bodies: In 350 of these cases, comparative tests were made with Lieben's, Legal's, Arnold's, Gerhardt's and Ehrlich's diazo tests, in a few Frommer's, Riegler's, Lipliawsky's and Lindemann's reaction were also employed. Quantitative acetone determinations were made in over 100 specimens by the Huppert-Messinger method. Oxybutyric acid was tested for by determining the levo-rotation after fermentation. Of the 350 specimens in which comparative tests were made, 250 were from diabetics; the remaining 100 were from

TABLE 4.—Case of Diabetes Mellitus.

Name.	Ten c. c. Urine + 1 c.c. Standard Ferric Chlorid Solution Diluted with Distilled Water to—	Diacetic Acid and Acetone in Terms of Acetone in Grams per Liter.
E. P. A.	Undiluted	0.200
R. B. . .	Undiluted	0.250
E. A. S..	Undiluted	0.500
J. W. T..	Undiluted	0.532
S. B. . .	20 c.c.	0.400
J. W. T.	20 c.c.	0.424
J. W. T.	20 c.c.	0.532
A. E. S...	30 c.c.	2.500
M. B. . .	30 c.c.	2.664
F. R. . .	40 c.c.	2.575
L. D. . .	50 c.c.	2.665
M. B. . .	50 c.c.	3.200
G. L. . .	60 c.c.	5.000
M. F. . .	90 c.c.	13.330
G. L. . .	120 c.c.	12.800

TABLE 8.—Case of Cyclic Vomiting.

Date, 1905	Acetone.		Diacetic Acid.		
	Lieben's.	Legal's.	Arnold's.	Gerhardt's.	
April 12	+	+	+	+	Height of Attack
April 13	+	+	+	0	Less severe.
April 14	+	0	0	0	Still better.
April 15	0	0	0	0	End of attack.

miscellaneous cases, including starvation, abdominal neoplasms, cyclic vomiting, pregnancy, operative cases, obesity, febrile (grippe, tonsillitis, typhoid, pneumonia, cerebrospinal meningitis) and normal cases.

The reactions finally selected on account of their relative delicacy and ease of application were as follows:

FOR ACETONE.

1. *Lieben's Test.*—Five c.c. of commercial hydrochloric acid were added to 50 c.c. of urine and distilled. To the first 5 c.c. of the dis-

tillate there are added 5 drops of a 30 per cent. solution of sodium hydrate and 10 drops of iodopotassic iodid solution. If acetone is present, a yellowish precipitate of iodoform will be thrown down which may be recognized macroscopically, or under the microscope if present only in traces. This will detect acetone when present only in traces found in normal urine, viz., under 0.020 gram to the liter. Unless special precautions are taken,[8] alcohol and aldehyd will precipitate iodoform in the same manner; therefore, this should be borne in mind as a possible error.

2. *Legal's Test.*—To 5 c.c. of the native urine there are added 5 drops of a freshly prepared 20 per cent. watery solution of sodium nitroprusside and 5 drops of a 30 per cent. solution of sodium hydrate. This is poured into a white porcelain dish and glacial acetic acid added, drop by drop. The development of a purplish color indicates the presence of acetone. This will detect acetone when present in amounts over 0.030 grams to the liter, i. e., whenever acetone is present in pathologic quantities. A positive Legal's reaction is also given by urines containing creatinin in considerable amounts, aldehyd and alcohol.

FOR DIACETIC ACID.

3. *Arnold's Test.*—Two solutions are necessary. The first solution is made by dissolving one gram of para-amido-aceto-phenon in 100 c.c. of distilled water and adding hydrochloric acid, drop by drop, until the solution, which at first is yellow, becomes colorless; an excess of the acid should be avoided. The second solution is a 1 per cent. watery solution of sodium nitrite. Mix 2 c.c. of the para-amido-aceto-phenon solution with 1 c.c. of the sodium nitrite solution; to this add 3 c.c. of the urine to be tested, then 3 drops of strong ammonia. This is poured into a white porcelain dish and an excess of concentrated hydrochloric acid is added. In the presence of diacetic acid a purplish violet color appears which may readily be seen against the white porcelain.[9]

In my hands this has proved the most delicate reaction for the detection of diacetic acid which we posses. Lipliawsky's modification takes a little more time and seems to be no more delicate. Arnold's test does not react to acetone or β-oxybutyric acid, nor is this color developed in the urine of patients taking salicylic acid compounds.

4. *Gerhardt's Test.*—In this test a stock solution of 50 grams of ferric-chlorid dissolved in 50 c.c. of distilled water is used. One cubic centimeter of this solution is added to 10 c.c. of urine. In the presence of diacetic acid, in considerable amounts, a purplish red color is developed.

This is not as delicate a test as Arnold's. Gerhardt's reaction also

occurs in the urine of patients taking the salicylic compounds, phenacetin, antipyrin, etc.

In my routine work I have come to make use of the above-mentioned four simple reactions. Frommer's test[10] has not, in my hands, proved satisfactory. It seems to answer fairly well to detect acetone when it is present in large amounts, but the color reaction is uncertain and exceedingly slow when only small quantities of acetone are present. Ehrlich's diazo reaction, as first pointed out by Munson and Oertel,[11] is a fairly good test for diacetic acid, but is neither as reliable nor as delicate as Gerhardt's test.[12] Riegler's test[13] for diacetic acid is less delicate than the ferric chlorid test. The same may be said of Lindemann's test.[14]

In the 500 specimens of urine examined, whenever diacetic acid was found, acetone was invariably present. A much smaller number were examined for oxybutyric acid; whenever this was present the specimen invariably contained both diacetic acid and acetone. I believe we may feel positive that whenever oxybutyric occurs in the urine it is always associated with acetone and diacetic acid. With an excretion of diacetic acid there is always an acetonuria. Reversely, however, we may have acetone without diacetic acid or oxybutyric acid. Or acetone and diacetic acid without the excretion of β-oxybutyric acid.

We have at present no satisfactory means of estimating the amount of diacetic acid in the urine. All quantitative estimations of acetone represent acetone plus diacetic acid (if this is present) in terms of acetone. Oxybutyric acid may be accurately estimated by a laborious process or may be roughly determined by the degree of polariscopic levorotation after fermentation.[15]

In the above series a great many quantitative acetone determinations were made with the purpose of obtaining, if possible, a simple method of following the increase and diminution clinically of the acetone bodies. A few of the typical results, which could be greatly extended if space would allow, are shown in Table 3.

From this table it is evident that there is a fairly definite relationship between the delicacy of the above reactions and the amount of diacetic acid and acetone present, estimated as acetone. This relationship holds good only for fairly fresh urines. After standing for two or three days diacetic acid is broken down into acetone and the amount of acetone estimated is greater than is indicated by the application of the above tests.

When we come to consider a simple method for estimating the acetone bodies when they are present in larger amounts, we meet with the difficulty that the relative amounts of acetone and diacetic acid in these

TABLE 5.—Case of Obesity (Reduction Treatment).

Date. 1906	Amount in 24 hours, c.c.	Specific Gravity.	Reaction.	Albumin.	Acetone.		Diacetic Acid.		Acetone, grams per liter.	Acetone, grams in 24 hours.	Urea, grams in 24 hours.	Weight, pounds.	
					Lieben's.	Legal's.	Arnold's	Gerhardt's.					
Jan. 29.	1825	1026	ac	0	+	0	0	0	0.040	0.073	25.5	241	Mixed diet unrestricted.
Feb. 4.	1550	1021	ac	0	+	+	+	0	. . .	. . .	15.5	237	No carbohydrates for 1 week.
Feb. 9.	1700	1019	ac	0	+	+	+	+	0.800	1.360	27.2	235	Fat-proteid + 100 gms. wheat bread.
Feb. 12.	1350	1025	ac	0	+	+	+	0	. . .	. .	24.2	233½	Fat-proteid + 200 gms. wheat bread.
Feb. 20.	1215	1022	ac	0	+	+	0	0	. . .	. . .	24.3	230	Fat-proteid + 3 slices rye bread and ½ grape fruit.
Mar. 2.	1320	1024	ac	0	+	+	0	0	0.100	0.132	26.4	226¼	Fat-proteid + 3 slices rye bread and ½ grape fruit.
Mar. 12.	1560	1023	ac	0	+	?	0	0	0.031	0.048	34.3	224⅜	Fat-proteid + 3 slices rye bread and 1 apple.
Mar. 26.	1440	1026	ac	0	+	0	0	0	0.019	0.027	34.6	228½	Fat-proteid + 3 slices rye bread and 1 apple.
Apr. 23.	1410	1021	ac	0	+	0	0	0	. . .	. . .	. .	216	Fat-proteid + 200 gms. wheat bread.

Loss of weight in 3 months 25 pounds.

TABLE 6.—Fever Case.

Date. 1906	Amount, 24 hours, c.c.	Specific Gravity.	Reaction.	Albumin.	Sugar.	Indican.	Diazo.	Acetone.		Diacetic Acid.		Acetone, per Liter.	Acetone 24 hours.	Temperature, F.	Diet.
								Lieben's.	Legal's.	Arnold's.	Gerhardt's.				
April 16.	—	1026	ac	0	0	0	0	+	+	+	+	1.132	. . .	101.5	Fluid diet.
April 18.	385	1023	ac	0	0	0	0	+	+	+	+	0.280	0.098	100.5	Fluid diet.
April 19.	440	1023	ac	0	0	0	tr	+	+	+	+	0.300	0.132	100	Fluid diet.
April 20.	770	1011	ac	0	0	0	0	+	+	+	0	0.125	0.096	99.8	Chop, eggs, etc.
April 23.	—	1016	ac	0	0	0	0	+	+	0	0	. . .	. . .	98.6	Full diet.

TABLE 7.—Very Severe Case of Diabetes Mellitus.

Date, 1904	Amount of Urine in 24 hours, c.c.	Specific Gravity.	Reaction.	Albumin.	Sugar.			Polarization.			Acetone.		Diacetic Acid.		Oxybutyric Acid.	Urea, Grams in 24 hours.	Ammonia, Grams in 24 hours.	Weight, Pounds.	Acetone.	
					Fehling's.	Fermentation.	Grams in 24 hours.	Before Fermentation.	After Fermentation.	Difference.	Lieben's.	Legal's.	Arnold's.	Gerhardt's.					Grams per Liter.	Grams in 24 hours.
Oct. 10, 1905	1380	1031	ac	0	+	+	69.0	. . . .	. . . .	. . .	+	+	0	0	. . .	23 5	1.17	130.	. . . .	. . . .
Mar. 13 .	1100	1028	ac	0	+	+	7 7	. . . .	. . .	. . .	+	+	+	+	. . .	30.8	.	130.	. . . .	. . . .
April 10. .	1000	1029	ac	0	+	+	6.9	. . .	. . . .	. . .	+	+	+	+	. . .	30.0	. .	137.	. . . .	. . . .
May 1. . .	1600	1028	ac	0	+	+	18.4	+0.3	−0.8	1.1	+	+	+	20†	+	.	. . .	136.5	0.500	0 800
May 8. . .	. . .	1029	ac	0	+	+	. . . .	+0.5	−1.2	1.7	+	+	+	30†	+	.	. . .	. . . .	1.333	. . . .
May 15. .	1200	1022	ac	0	+	+	. . . .	. . . .	. . . .	. . .	+	+	+	20†	. . .	. .	. . .	. . . .	0.598	0.657
June 5. .	1300	1028	ac	0	+	+	20 9	. . . .	. . . .	. . .	+	+	+	20†	. . .	. . .	. . .	136.	0.856	1.113
Dec. 18, 1906	1500	1025	ac	0	+	+	30.0	. . . .	. . . .	. . .	+	+	+	20†	. . .	19.5	. . .	128.5	0.700	1.050
Jan. 1. .	. .	1030	ac	0	+	+	. . . .	. . . .	. . .	. . .	+	+	+	30†	. . .	. . .	. . .	. . . .	0.664	. . . .
Jan. 8. .	1560	1030	ac	0	+	+	9.4	. . .	. . . .	. . .	+	+	+	50†	. . .	21.8	. . .	127.	3.200	4.992
Mar. 19 .	. . .	1027	ac	tr.	+	+	. . . .	. . . .	. . . .	. . .	+	+	+	20†	. . .	. . .	. . .	126.	0.800	. . . .
May 31. .	. .	1023	ac	0	+	+	. . . .	. . . .	. . . .	. . .	+	+	+	120†	. . .	20.7	. . .	111.	12.800	. . . .
June 4. .	2300	1023	ac	tr.	+	+	143 8	. . .	. . . .	. . .	+	+	+	60†	. . .	. .	. . .	. . . .	6.400	14.720
June 11. .	3210	1024	ac	tr.+	+	+	106.9	+3.2	−0.9	4.1	+	+	+	60†	57.8	32 1	6.55	108 2	5.000	16.050
July 7. .	2940	1029	ac	tr.	+	+	124.0	+3.7	−0.5	4.2	+	+	+	40†	29.4	18.8	3.68	106.0		
July 13 .	1900	1026	ac	tr.	+	+	45.6	+1.4	−1.0	2.4	+	+	+	50†	38.0	20 0	4 39	105.0		
July 29 .	3340	1028	ac	tr.	+	+	100 0	. . . .	. . . .	. . .	+	+	+	100†						
Aug. 14 .	3000	1025	ac	tr.	+	+	81.0	. . .	. . . .	. . .	+	+	. .	70†						
Sept. 1.	3700	1025	ac	tr.	+	+	130.0	. . . .	. . . .	. . .	+	+	. .	80†						

Died in coma, Sept. 15, 1906. † Number of cubic centimeters to which Gerhard's test was diluted as described.

cases is very variable. A rough idea, however, can be obtained in the following manner:

To 10 c.c. of the urine to be tested is added 1 c.c. of Gerhardt's test solution of ferric chlorid (made as described above). This is thoroughly mixed and allowed to stand for about two minutes (to permit the color reaction to fully develop). Then filter into a test-tube, one-half inch in diameter, and compare the color with a similar test-tube filled with the standard solution of ferric chlorid described above. If the color of the urine mixture is darker than that of the ferric chlorid solution, distilled water is added until the color is approximately of the same depth as that of the ferric chlorid solution.

From Table 4, made from the results obtained from a number of specimens examined by this method, a rough idea may be had of the amount of acetone and diacetic acid in terms of acetone which such dilutions indicate.

The practical application of this method is conducted in the following manner: The urine under examination is tested by Gerhardt's reaction. If this is positive, we know that diacetic acid and acetone are present in an amount in terms of acetone in excess of 0.200 gram per liter. If there is a strong Gerhardt's reaction, we dilute the test solution in the manner described above until the color approximates that of the standard ferric-chlorid solution.

If the final dilution indicates an acetone content of half a gram per liter or over, we may be reasonably sure that oxybutyric acid is present and may proceed to its determination by means of the polariscope. If Gerhardt's test is negative, we apply successively Arnold's, Legal's and Lieben's tests, in the order named. A positive Arnold's reaction indicates something over 0.100 gram of acetone per liter. A positive Legal's reaction indicates 0.030 gram of acetone per liter. Lieben's test, if positive while Legal's is negative, indicates the presence of acetone in an amount within the normal limits.

Lieben's.	Legal's.	Arnold's.	Gerhardt's.	Amount of Acetone in Gram per Liter.
Positive.	0	0	0	Less than 0.030
—	Positive.	0	0	0.030 to 0.100
—	—	Positive.	0	0.100 to 0.200
—	—	—	Positive.	More than 0.200

The above tests, with the exception of the polariscopic determination of oxybutyric acid and the distillation required by Lieben's test, may easily be completed inside of ten minutes.

Tables 5, 6, 7 and 8 indicate the method of recording cases and the comparative results obtained by actual quantitative determinations of acetone by the Huppert-Messinger method.

I wish to express my obligation to Dr. E. G. Janeway, in whose laboratory this work was conducted and to whom I am indebted for a large part of the material on which these observations were made.

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9. Wien. klin. Wchnschr., 1899, p. 541.
10. Berl. klin. Wchnschr., 1905, xxxii, p. 1008.
11. N. York M. J., 1893, lvii, p. 127.
12. The diazo reaction as found in typhoid fever is not usually due to the presence of diacetic acid, as Oertel and Munson claimed. It may occasionally be due to diacetic acid, but usually is due to some other substance.
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14. München. med. Wchnschr., 1905, p. 1386.
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EXPERIMENTAL OBSERVATIONS ON SECRETIN.

WITH SPECIAL REFERENCE TO DIABETES AND MALNUTRITION.*

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The work of Bayliss and Starling† in ascribing pancreatic activity to so-called "secretin," a product of union of the acid chyme and intestinal epithelium, has opened a new field of research in certain branches of pathologic physiology. It has been known for some time that the introduction of acid into the duodenum would be followed by a flow of pancreatic juice, but this had always been ascribed, even by Pawlow, to a nervous mechanism. It remained for Bayliss and Starling to show, by a series of elaborate experiments in which they completely separated the gland from all innervation, that the pancreas responded to something which was formed when the hydrochloric acid of the chyme came in contact with the mucosa of the upper part of the intestine.

This substance, they proved, was normally absorbed where formed, and carried by the blood to the pancreas, which it at once caused to secrete. Certain other substances were found to unite similarly with the mucosa and produced the same results. The ultimate nature of this exciting agent is not yet known, but it appears to be a fairly stable chemical compound which can be extracted with alcohol and resists boiling, proving quite conclusively that it is not in the class of ferments, as we ordinarily understand that term. The discoverers of this compound named it secretin, and to the contributory factor resident in the epithelium they gave the name prosecretin.

The question of glandular action by chemical messenger or "hormone" is one of much importance and possibly of wide application to many physiologic processes hitherto poorly understood, especially where no clearly demonstrable nervous mechanism is concerned; thus Edkins[1] has described an analogous mechanism which seems responsible, in some part, for gastric secretion.

In connection with secretin, it has been thought by some that since

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† Recent Advances in Physiology of Digestion, by E. H. Starling, Chicago; W. T. Keener & Co., 1906.

1. Jour. Anat. and Physiol., Lond., 1906, xxxiv, 133.

it causes an external secretion of the pancreas, it might also induce an internal secretion having some relation to diabetes. Work has been done on this line to which we shall have occasion to refer later. It seemed to the present authors, however, that apart from any specific property of secretin or prosecretin, its precursor in the intestinal mucous membrane, such a fundamental feature of pancreatic activity must be of wider significance. To find pancreatic secretion referable to a definite and well localized substance occurring in a certain place only, suggests the query, "What would happen if this substance were lacking?" As a function of the animal economy it must be subject to disturbances, and such disturbances might be of the utmost importance to health.

Cohnheim[2, 3] has shown that perhaps the most important of our digestive functions, proteolytic digestion, takes place not alone by virtue of the pancreatic juice, but also by means of certain other ferments (which act in the mucosa of the small intestine), and Vernon[4] seems to have proved that this same ferment action occurs in the other tissues of the body as well; but, however this may widen our conceptions of tissue destruction and construction, there can be no doubt of the prime importance of the pancreas and its juice for the purposes of intestinal digestion, not only of proteid, but also of the other elements of our diet. A failure of this secretion would, in the nature of things, lead us to expect a condition of perverted nutrition. It is true that Pawlow has produced permanent pancreatic fistulæ in dogs which survived for some time after the operation, but they were fed on special diet, with special care, in order that digestion and assimilation might take place.

With these facts in mind it occurred to us that it might be possible to demonstrate a deficiency or absence of these excitors of pancreatic activity in various conditions of malnutrition, and, perhaps, establish some etiologic relationship. Edsall[5] proposes the same thing in connection with some suggestive work by him on the rôle played in these same perverted states by the ferment eropsin, mentioned above as being resident in the small intestine and first discovered by Cohnheim. Some time since we began our work Wentworth[6] reported some cases of marasmus in which he found no evidence of prosecretin, and he regards this deficiency as the cause of the disease. We will refer to this work later. Bainbridge and Beddard[7] have reported six cases of diabetes which they investigated for the presence of prosecretin with similar negative results.

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We originally meant to work on the line of pathologic physiology indicated above, but on attempting to establish some standard of normal action we encountered so many points of interest and difficulty that we had first to undertake a considerable series of purely physiologic experiments. It is the result of these, chiefly, that we wish to discuss.

We began, therefore, with efforts to excite the pancreas in dogs in which a temporary pancreatic fistula had been formed. We injected into them, through either the jugular vein or a vein of the hind leg, material obtained at the autopsy table, from various pathologic subjects. Our methods of work were essentially as outlined by Bayliss and Starling, and as far as possible, except where otherwise indicated, we endeavored to duplicate the conditions of each experiment in the attempt to be uniform. The human autopsy material was obtained in most instances as soon as possible after death, and the periods elapsing between death, autopsy and preparation of extract noted. They appear in the protocols.

The mucous membrane was scraped from the upper four to six feet of the small intestine with a piece of plate glass having a smooth edge, after the gut had been opened, washed in plain tap water and drained as well as possible. It was found that the nature of the gut varies considerably in different individuals, making it very difficult at times to remove the epithelial lining. In certain elderly subjects the membrane seems to be firmly adherent, requiring firm pressure in scraping to separate it, while in younger individuals it is removed with less difficulty, though rarely giving much bulk of material. In this respect the human gut differs radically from that of the dog, sheep and calf, from all of which, preparations were made. Although the intestine of a dog is less in lumen than that of a human being, the epithelium is not only relatively more abundant but actually so as well, and, furthermore, it can be removed with the greatest ease by light pressure, making in practically every case examined a greater bulk of scrapings than that from a human being. Not only is this true of dogs, but also of sheep and calves, in the former of which the gut is very much smaller both in lumen and thickness than in man, and it is also scraped more easily.

The membrane thus removed from the upper four feet of the small intestine, except where six feet were used, as noted in the protocols, was covered with a small amount of dilute hydrochloric acid and ground up with sand in a mortar. Inadvertently, acid of slightly less than 0.2 per cent. strength was used in the early experiments instead of 0.4 per cent. strength, which was adopted later, as noted.

The mortar contents, after being ground for about ten minutes, were slightly more diluted with as little acid as possible (the amounts are

given in each case), and transferred to a porcelain dish, where they were brought to boiling. A few drops of fairly strong caustic soda solution were then added, while stirring, until litmus paper showed faint alkalinity, and then the reaction was made slightly acid with glacial acetic acid, diluted one to three or four with water. A very few drops sufficed for this, and with the precipitation of the precipitable proteids the supernatant liquid, which had before been thick and opaque, became clear and could be decanted. In the earlier experiments the whole contents of the porcelain dish were strained through unbleached muslin by squeezing. It was found, however, that even with most of the proteid constituents precipitated as above, it was very difficult to filter the solution thus obtained. By the time it ran fairly clear and was free from opacity, even with a suction filter, the delay was so great and the amount of fluid obtained was so slight that we feared oxidation would render the preparation less active, if not inert, as stated by Bayliss and Starling. Later preparations were, therefore, made by simply decanting from the porcelain dish after addition of acetic acid and filtering this hot liquid quickly through coarse paper. At different times filtrates at varying stages of preparation were used, some of great opacity and some clear, while the supernatant fluid was used at other times without further treatment; but as far as could be seen the active properties were contained no more in one than in the others. Filtration, therefore, seems not to affect the activity of the extract, though we can not insist on this point as yet. The above solutions were then transferred to small Erlenmeyer flasks, sterilized in an Arnold steam sterilizer and used as soon as possible. After injection unused residues were resterilized for subsequent use.

The mechanical problems involved in making a pancreatic fistula in a dog are peculiar and deserve a short notice. The incision, like all physiologic incisions, is of importance secondary to the question of satisfactory exposure. Our method was to make a two-inch incision directly over the pancreas well to the right of the mid-line. The lower end of that portion of the pancreas which is closely attached to the intestine is withdrawn, together with the intestine. One can then locate the duct by palpating between the thumb and finger the tissue which lies between the pancreas and the intestine. The duct will be found lying within an inch from the lower end of the attached portion. The duct is then freed by careful blunt dissection and traced into the intestinal wall; a longitudinal incision is made in the duct, as far as possible into the intestinal wall, and the canula introduced and tied in place by means of a ligature, which passes entirely around the duct. A form of canula which has

given us satisfaction is that made with a tip of platinum fused into a graduated glass tube.

The necessity of adopting this technic evolved itself during the course of the work. The reason for exposing the duct external to the intestine is that the pancreas is one of the most delicate organs of the body, and attempts to introduce an adequate canula through the normal opening of the duct cause hemorrhages from the mucous membrane of the intestine. The actual mouth of the duct is smaller than the lumen as a whole, and hemorrhage is prone to occur also from the mucous membrane of the duct itself. The hemorrhages thus caused are persistent and induce coagulation of the pancreatic secretion. It is advisable to trace the duct well into the intestinal wall because part of the duct which is common to the upper and lower ends of the pancreas is extremely short; often so short, in fact, as to preclude tying a canula in place without excluding, by the ligature, the duct of the lower third of the organ.

We were led to the adoption of a canula with a tip of platinum because that metal can be wrought very thin and still possess ample strength. The lumen of the tip can then be made as great as the lumen of the canula, and, indeed, but little smaller than the lumen of the duct itself. On the outside of the extreme tip of the canula is a small ridge for a ligature, which is necessary to prevent the canula from slipping out of place during movements of respiration and peristalsis.

Extreme care must be taken in manipulating the pancreas, as very small hemorrhages frequently occur from the wall of the duct, and the admixture of the least amount of serum with the pancreatic secretion may cause a coagulum which will effectually block the canula. This can be materially prevented by coating the interior of the platinum tip and the lower end of the glass with paraffin. The caliber of the duct varies so greatly that we have two sizes of canulæ, using always that caliber which most closely approximates the caliber of the duct.

It will be seen from a study of the protocols that our first attempts with human preparations injected into dogs were failures, despite the fact that every possible care was exercised to have the conditions of preparation of extracts identical with those in preparation of extracts from dogs. Of a total of nine human cases from which we tried to obtain active extracts, in only two did we meet with certain success. The dog extracts, on the contrary, as also the sheep and calf extracts, were obtained active at the first attempt. We have not recorded a single instance of failure to obtain a very violent and pronounced reaction from them, though in many of the experiments the acidity of the extract more

nearly approached the acidity of the chyme in man than that in lower animals.*

It was noted that the extracts from man's intestines were harder to filter than those of animals, and after several failures we decided not to attempt much filtration (for which considerable liquid was required), but to use less fluid and decant sufficient for use from this more concentrated preparation. This was done, and, as seen in the records, a response was obtained on injection. Active animal preparations were obtained from both 0.2 and 0.4 per cent. strength hydrochloric acid, but in our series, human preparations of undoubted activity were obtained only from the acid of 0.2 per cent. strength.

In making our first controls we used secretin extracts made from dogs, and later on we made extracts from the sheep and calf, just mentioned, in order to satisfy ourselves that there was no specificity of secretin for any particular genus. The response given by the sheep extract was, perhaps, the most violent and pronounced of any witnessed, and it seems most improbable that a difference in the nature of the human secretin, *per se,* was in any way responsible for the failures following its injection.

During the course of the experiments fresh extracts were prepared from dogs, solely as controls of known activity, in testing human preparations under consideration. It, therefore, seems that although the acid extract of human intestinal membrane is higher in those presumably proteid and gelatinous constituents which make it difficult of filtration, the human intestine is not only relatively but actually lower in its content of prosecretin than is the intestine of some lower animals. The greater bulk of epithelium which can be removed from the animal gut doubtless accounts for this, and it appears that this is, perhaps, a provision of Nature, in keeping with other differences shown in the various species. For example, the acidity of the gastric secretion in a dog is greatly in excess of that in man, reaching 0.5 per cent. in order that he may digest the large pieces of meat swallowed without mastication. R. Meade Smith[8] gives a series of analyses of gastric contents in man, dog, sheep and horse, of which the hydrochloric acid in man, in 1,000 parts, was 3.19; in sheep, 4.05; in a horse (diet of oats), 4.9; in a dog, 17.13, from which it will be seen how greatly in excess of the human average all of these are. It seems probable, therefore, that the greater provision of epithelium (and, therefore, presumably of prosecretin) is to keep pace

* Since writing the above, we have made additional secretin preparations, in another connection, from about eight more dogs, and in every instance have obtained extracts of great activity.

8. Physiology of the Domestic Animals, 1889.

with this large amount of acid and to excite a copious and equal alkaline secretion from the pancreas. Certain it is that under the above conditions the preparation of an active extract of secretin is more difficult from man than from animals, and it may be for the reason stated above.

We intended, at one time, to take equal weighted amounts of intestinal scrapings from man and dog and dilute them with large and equal amounts of acid. We hoped to show by this that, whereas, the dog epithelium would yield an active extract even with considerable dilution, none would be obtained from the human, for the above reason. Unfortunately, however, we had to stop work temporarily at this point, but the same fact is indicated to all intents and purposes by the last human case tried, reference to which will show that only 65 c.c. hydrochloric acid were used. The preparation was inactive, or at best but slightly and very questionably active, whereas a coincident extract of a dog was diluted with over twice that amount of acid and still gave a violent response. The respective amounts of intestinal epithelium removed were not weighed, but were roughly comparable in bulk.*

In view, therefore, of the difficulties recorded in obtaining active human preparations, we feel that caution should be exercised in basing conclusions on negative results which are not fully controlled and in which the flow of juice is not accurately measured. The measurement is not so much for comparison between the individual animals injected, because each is (within limits) a law unto itself as to the rapidity and amount of flow, but for each case there should first be established some dependable standard of secretion as a normal on which can be based exacerbations due to injections.

It seems that entirely apart from differences in the sizes of animals, which would determine variations in flow, the rate of flow and amount of pancreatic juice obtained vary with the period of digestion. It thus seems easier to excite a flow of pancreatic juice when the animal has been fed within a few hours than when it is fasting. Furthermore, the copious flow thus obtained is calculated better to prevent the formation of clots which form so readily both in the canula and within the excretory duct itself, as mentioned above. Consequently, in our later experiments, we used dogs which had been recently fed.

For the above reasons and for others which will appear later we are led to accept with reservation, the finality of Wentworth's findings in

* Since above was written we have obtained a violently active preparation from a dog's intestines, with a dilution of 310 c.c. $\frac{4}{10}$ N HCl.

cases of malnutrition because we know how easy it is to obtain an inactive extract in a subject from which there is every *a priori* reason to expect a response. To turn to his interesting work in which he records an absence of secretin in a number of cases of marasmus examined, several points call for consideration.

In the first place, he details a series of cases of marasmus and some also of new-born children, in which he finds secretin absent. He believes this deficiency of secretin to be due to an insufficient quantity of hydrochloric acid in the stomach of these children, this, in turn, being caused by the fact that the milk of each species has some specific element which is necessary to its perfect digestion by that species, and in the case of marantic human infants fed on cow's milk, for example, this is lacking. Without questioning the evidence in favor of the latter contention, in this particular connection, let us consider the reported absence of secretin in the newborn.

The citation of this deficiency is evidence, it seems to us, in support not of the unknown and unlikely possibility that a child is thereby unqualified for pancreatic digestion of its mother's milk (which we know clinically is not the case), but rather that this "absence" of secretin is another instance of the difficulty of obtaining it under a considerable variety of circumstances and in, perhaps, a number of pathologic conditions. In point of fact, secretin has been found in both the embryo and the newborn, and in the human as well as in the animal species,[9, 10] which would go to prove that some of the many factors to which we refer as making secretin at times difficult of extraction, have been operative with Wentworth, not only in these children at birth, but, perhaps, as well in those cases of malnutrition on which he bases his report. Failure to detect it in the newborn seems an evidence against the very specificity of its absence in pure marasmus.

In both of these conditions, as we have tried to indicate, the evidence for the absence of secretin as against a frequent general difficulty of its extraction under many circumstances, is very incomplete. We feel, therefore, that the whole question of the activities of digestion is much too complicated to justify the assumption at present that marasmus is referable to a factor so difficult of exact definition as the absence of secretin.

That this absence should, furthermore, be dependent on a deficiency of hydrochloric acid, and this, in turn, on a specificity of milk, seems an hypothesis calculated beyond the facts at our command. With our pres-

9. Camus: Compt. rend. Soc. de biol., Par., 1906, lxi, 59.

10. Hallion et Lequeux: Id., 33.

ent knowledge of the subject, we feel that the properties and activities of secretin are much too unmapped and too little understood for us intelligently to ascribe a great morbid state to its deficiency alone, and when it comes to building further on this foundation the question becomes one of almost pure hypothesis. As a general principle, we know that the interdependence of the various digestive and assimilative processes is against such specificity, and we are beginning to recognize this interdependence as much wider than was hitherto thought. In illustration of this Abelmann and Sandmeyer[11] have shown that complete extirpation of the pancreas from dogs is followed by the absorption of 33 to 45 per cent. of non-emulsified fat. Again, if the connection between the pancreas and the intestine is cut off completely and permanently, the pancreas itself remaining wholly or partially in the system, it is found that the absorption of fat may be maintained (80 per cent.) for a considerable length of time.[12] The work of Brücke, Voit and Bauer, Heidenhain, Friedländer and others[13] abundantly proves that the protein of flesh, as well as both serum and egg albumin, may be, in part at least, absorbed as such; from which alone we see the abundant provision of Nature against the weakness of a single part in her complicated system of nutrition.

That some disturbance of the amount of secretin may be a link in the chain of events which produces infantile atrophy we readily grant, and, in fact, had started work on the basis of an analogous hypothesis; but that the other links of the chain are known, or that a causative deficiency or absence of secretin has been established in that interesting condition, we can not at present believe.

An examination of the work of Bainbridge and Beddard on diabetics will show that they measured the flow of juice in drops and cubic centimeters. This method of measurement seems to be open to some criticism. The output of such an organ as the pancreas is, in the nature of things, a relatively small quantity, and exacerbations of flow can not be appreciated within small limits when the index is so crude. The method of Bayliss and Starling is certainly the most graphic and satisfactory for recording the flow, where at all practicable, but it requires that the tube be filled and the juice allowed to drop on a recording tambour. With weak preparations or where, for any reason, there is difficulty in obtaining a steady flow, the first output may be ample to indicate the activity of a given preparation and yet quite insufficient to fill a canula of five

11. von Noorden: Metabolism and Practical Medicine, i, 30.
12. Sandmeyer, Abelmann, Rosenberg, loc. cit.
13. Von Noorden: Metabolism and Practical Medicine, i, 19.

inches, much less to drop from the end of it. For these reasons, we found a graduated canula better adapted to our needs.

In regard to the estimates of flow given by Bainbridge and Beddard, it can be said that with an actively functionating gland there is, at most times, a flow, and the statement that a drop or a cubic centimeter resulted from an injection is somewhat questionable information as to whether the gland was stimulated or not, in the absence of data giving the normal rate of secretion. It assumes that the tube must be full at all times, but from such a tube drops might fall with varying speed, due, for example, to changes in blood pressure, which is appreciably lowered by the injection. Again, if such a tube be filled, more powerful respiration or any unusual movement of the animal may induce a change of level in the tube and consequently cause a drop to fall. Bainbridge and Beddard give no data of time elapsed when recording flows which took place or failed to take place after injection. In Case 5 of their diabetic series they obtained 0.6 c.c., a response greater than that from some of their normal preparations, as, for example, that from a normal cat, and yet this response is recorded as moderate. Case 6 gave persistently one drop in response, and Case 4 gave two drops on two occasions, and it seems to us that in both instances these were indications of responses which might have been more marked had there been, perhaps, less dilution of the secretin, or more regard for the relative difficulty under many circumstances of extracting it from human intestines. A deduction from this that secretin is diminished in amount in these particular cases seems to us hardly to be justifiable. The same authors, unfortunately, omit also to give the amounts of juice secreted in their series of controls, and state merely that they were abundant, fair or moderate, by which very little comparison can be made with their later work. Bainbridge and Beddard conclude that "in only one of six cases of severe diabetes was prosecretin present in amount approximating the normal," and in the other five cases they say that prosecretin "was either absent or present in very small quantities," but we feel that without more accurate methods of establishing a standard of reaction and of measuring the flow such results must be accepted with reserve. Bainbridge and Beddard speak, for example, of a maximum and minimum dose without stating what either is, and it would be of interest to know the dilution with acid of the intestinal scrapings. Other observers, as Moore, Edie and Abrams, quote the above work as evidence that secretin is absent in many cases of diabetes, but it may well be that the failure to react was at times due to some of the factors which have prevented us from getting responses. It is to be remembered, furthermore, that in an individual the subject of a chronic

wasting disease, such as diabetes or marasmus, the intestinal epithelium shares with the other bodily structures a degree of atrophy, perhaps secondarily, and the reduced bulk may require different treatment to develop the properties still present within it. This, again, may have been the cause of a certain number of failures.

Therefore, we are forced to conclude that, while the absence or deficiency of secretin may be a factor in certain varieties of diabetes, the evidence of this, hitherto adduced, is not convincing to all of those who have worked on the pancreas and its excitation.

In order to obviate the possibility that postmortem change was responsible for some of our failures, we killed a dog, kept the body on ice for thirty-six hours and then removed the upper part of the small intestine. This we kept on ice for another fourteen hours, and then worked up as usual, with the result to be mentioned presently. It had occurred to us also that another possible source of failure was the necessarily restricted diet of most hospital patients who come to autopsy, so that the dog above mentioned was fed for about one week prior to death on a pure milk diet. Evidence of the fact that he had been well starved was the condition of the stomach and small intestine, both of which were full of sawdust, which had formed part of his bedding. He had, of course, attempted to satisfy his hunger by eating it. The extracts from the intestine of this animal were powerfully active.

We wish to emphasize the fact that in testing the human preparation a response was in all cases first obtained by means of a known active extract in order to obviate failure from causes other than inactivity of the preparation in question, and following its injection known active extracts were again used wherever possible. This inclusion of an inactive human preparation between two plainly active animal extracts would seem to narrow down the failure of response to some feature of the preparation itself.

Another thought which suggested itself was that the strength of the acid used in working up the preparations might be responsible for some negative results, but reference to the records will show that we eventually obtained active extracts from dogs, with both weak and strong hydrochloric acid, as referred to earlier, so that the formation of secretin apparently is not dependent on the peculiar acidity of the chyme in any particular animal. It would appear probable also that neither fasting nor the nature of the diet has any marked influence on the qualities of an extract.

Some of our active preparations were used a number of times, and we found that if kept sterile, an extract will retain its efficiency for many

weeks, though it deteriorates slowly, as stated by Bayliss and Starling. The reactions caused by the injection of equal amounts grow less intense as time goes on and finally cease altogether. One of our extracts showed activity for at least nine weeks, which is the longest recorded period of which we have any knowledge.

Finally, we come to the consideration of those human cases in which we found secretin positively present. They were two in number, respectively Cases 8 and 10, out of a total of nine examined. In two other cases there was some evidence that it was present also, though we were not convinced of the fact at the time of the experiment. They were Cases 14 and 15. It may be, of course, that failure to demonstrate any secretin in the remaining cases was due to the fact that these cases presented some of the pathologic conditions originally the subject of our investigation. This can not be asserted, however, with our present knowledge of the subject. As a corollary to this is the record of the presence of secretin in a case of pulmonary phthisis (Case 8) and a case of cholelithiasis with jaundice and cardiorenal disease (Case 10). Two cases are, of course, inadequate in number to warrant definite conclusions, but it might seem from them that the absence of secretin is not a causative or accompanying feature of these diseases.

It is of some interest to consider the nature of the various cases in which no secretin could be detected positively after repeated injection of various preparations from them into different dogs (which responded to other stimuli). These cases represented, respectively, the following diseases: tabes dorsalis, lobar pneumonia, fracture of the skull, pseudohypertrophic muscular dystrophy complicated by phthisis, uremia (or possibly epilepsy), phthisis, and erysipelas following debauch.

It will be noted that one of our active extracts was from a case of phthisis (Case 8), and yet we were unable to get positive results from two other instances of this disease. In one of them (Case 14) there was some evidence of a response, but, as indicated above, we do not feel warranted in regarding it as certain. The other was complicated by muscular dystrophy, which is a rather suggestive result, though, of course, by itself of no value whatever. It is conceivable, however, that this last interesting and baffling condition may be found to be due to some factor, perhaps as yet undiscovered, which affects the construction of tissue. In this connection, one of the present authors has made some attempt, as yet unsuccessful on account of the paucity of cases and the difficulty of the procedure, to investigate the proteolytic and proteoconstructive ferments found by Vernon to be present in nearly all tissues. An absence of one or more of these from muscular tissue might possibly stand in some

relation, primarily or secondarily, to the well known metamorphoses of this disease.

We have been unable to account satisfactorily for an initial spurt in the flow of juice which often occurs when a canula is first introduced successfully into the common duct. The more ready and the quicker the introduction, the more marked the initial spurt, which in a minute or so subsides to what may be called the normal rate of flow. Bayliss and Starling state that there seems to be little or no diminution in activity after prolonged stimulation of the pancreas with secretin, and they quote one case which seemed to have lost an activity after stimulation for a total of 8 hours. Without questioning this finding, our experience has been that the pancreas reacts best to early injections, and that after repeated excitations the response is less marked in amount and violence. It would seem much more in the nature of things that the organ should become exhausted in time, but we made no observations directly to this end and can not, therefore, offer anything more positive on this point.

There can be no question that there remain a great many features in connection with this interesting subject of pancreatic excitation which call for investigation. It is our hope to pursue some of them in the near future, and it is only because of the growing activity in this line of work as well as the evident need for accurate observations that we wish to publish, at this time, the results of our own experience.

CONCLUSIONS.

1. There would seem to be some factor which makes the preparation of secretin from human intestines more difficult than from the intestines of some animals.

2. This factor may depend on the relatively great abundance of membrane in these animals and consequently greater amount of prosecretin.

3. The abundance of mucosa may be, in part, a provision of Nature in order that the strongly acid chyme of some animals may meet with a quantity of pancreatic juice sufficient to neutralize it and effect digestion.

4. Active preparations of secretin can be made with hydrochloric acid of widely varying strengths, and activity, *in vivo*, is apparently not dependent on the peculiar acidity of the chyme in any particular animal.

5. Dieting and fasting seem to have no appreciable effect on the activity of an extract.

6. Time elapsed between death and the preparation of the extract (within limits) does not seem to be a factor.

7. Caution should be exercised in basing conclusions on work not thoroughly controlled, as the demonstration of secretin may be prevented by many factors not easy of determination.

8. In investigating for its presence, the normal flow and the exacerbations should be measured carefully by means of some accurate gauge, such as the rate of flow through an accurately spaced canula or by the recording of time drops with a tambour.

9. The evidence so far adduced that secretin is absent in some varieties of diabetes does not seem conclusive.

10. The specific absence or deficiency of secretin in marasmus seems to remain as yet unproven.

We wish to express our thanks to Dr. A. J. Smith, Dr. Samuel Leopold and Dr. L'Engle for courtesies shown at the autopsy table in obtaining material, and especially to Dr. David L. Edsall for his helpful interest in the work.

PROTOCOLS.

It should be stated that the flow of juice was at times hard to record, because after introducing the canula into the pancreatic duct, the intestine and attached duct were replaced in the abdominal cavity where they were more or less out of reach and somewhat covered over. The canula generally became partly coated with blood, which often obscured both the markings upon it and the juice within it. The deep position within the abdomen of the duct and proximal end of the canula increased this difficulty, so that it became necessary at times to count from the outer end of the tube instead of from the inner. Where this occurred it is so stated.

The caliber of the canulæ used varied somewhat as did the markings on them. In cases where the flow was slow, fine gradations were required to measure its advance. In cases where it was very rapid, we were often unable to note its rate by the one-eighth inch gradations alone and had time to measure the progress at intervals of five divisions only.

When the canula became filled, it was emptied by sucking through a still finer glass tube, introduced within it to the lowest gradation desired.

The notes of our cases are as they were made at the time. The strength of acidity of the preparations was not measured regularly, but from several titrations, made at various times, they approximated the following:

$$8 \text{ cc. secretin extract} = 0.1 \text{ cc.} - \frac{4}{10} \text{ N NaOH.}$$

In our first experiments, having then no controls of known activity, we established a flow of juice by the injection into the duodenum of 25 c.c. of $-\frac{4}{10}$ N HCl.

Several attempts were made to obtain permanent pancreatic fistulæ in dogs, but the difficulties in the way of the proper after-care of the animals caused us to work with temporary fistulæ instead. Our animals were kept under complete ether anesthesia, and at the end of the experiments they were killed.

We desire to give our observations at length, because they seem to us to show the difficulty in reaching dependable conclusions even when every effort is made to be accurate. That this difficulty must be greater with estimations which are more approximate, is self-evident.

CASE 1.—Feb. 28, 1907. A. M., male, white, age 53 years. Philadelphia Hospital. Died, 7:45 p. m., February 27. Autopsy performed 4 p. m., February 28.

Pathologic Diagnosis: Emphysema and edema of lungs; brown atrophy of heart; chronic cystitis; pyemic kidney; hypertrophy of prostate; tabes dorsalis.

Thirty-six hours after death, upper four feet of intestine extracted and put over night in ice-chest. Scraped with much difficulty, as it was very tough. Whole quantity (what could be held in man's hand, perhaps) covered with 0.2 per cent. HCl (100 c.c.) and ground in a mortar with sand. About 300 c.c. HCl then added; whole squeezed through mesh, filtered and then sterilized in autoclave.

No reactions were obtained with this preparation.

CASE 2.—March 31, 1907. J. C., male, colored, age 42 years. Philadelphia Hospital. Died, 4 a. m., March 31. Autopsy performed, 1:30 p. m. same day. Pathologic Diagnosis: Croupous pneumonia, gray stage, with cavity from poor resolution; acute fibrinous and chronic adhesive pleurisy; chronic adhesive perisplenitis and chronic interstitial splenitis; fatty infiltration of liver and cholelithiasis; acute parenchymatous nephritis, superadded to slightly fibroid kidney.

Upper four feet of intestine used; 125 c.c. 0.2 per cent. HCl; boiled, neutralized, acidified, etc., at night, March 31, 1907.

April 1, 1907, almost impossible to filter; most of solution lost in attempt; about 40 c.c. left, which were used. No result, though good reactions were obtained with 0.2 per cent. HCl thrown into duodenum twice; secretion of juice unusually free, both when canula first introduced and when HCl was injected into duodenum; presumably because of recent feeding, as gut at first was full of food.

CASE 3.—April 5, 1907. Large black bitch, very fat, killed with gas. No previous operation on animal. Four feet of intestine cut out (with pylorus) within one-half hour of death, and scraped, ground and diluted with 225 c.c. of 0.2 per cent. HCl; some fat in filtrate, which filtered slowly but better than last. Sterilized and finally free from evident fat.

CASE 4.—April 16, 1907. C. M., female, white, age 52 years. Philadelphia Hospital. Died, 8:30 p. m., April 14. Autopsy performed 5:30 p. m., April 15. Coroner's case. Pathologic Diagnosis: Chronic parenchymatous nephritis; tuberculosis of lungs; chronic myocarditis; right-sided subdural hemorrhage. The tuberculous involvement was relatively slight and in no way the cause of death. Clinical Diagnosis: Fracture of skull.

Intestines easily scraped, normal in appearance; 250 c.c. HCl used; run through quite rapidly and not filtered perfectly clear in order to avoid possible oxidation. No reactions were obtained with this preparation.

CASE 5.—April 17, 1907. Medium large, male, woolly dog. Ulcers and worms in intestines; dog had been bled five days before; killed 12:30 p. m. Intestines worked up instantly.

CASE 6.—April 23, 1907. E. B., male, white, age 15 years. Philadelphia Hospital. Died, 5:30 a. m., April 22. Autopsy performed about 4 p. m. same day. Pathologic Diagnosis: Fibrinous pleuritis of right side; fibrous pleuritis of left side; purulent bronchitis, peribronchial pneumonia, pseudo-lobar pneumonia, edema, congestion and emphysema of lungs; subacute nephritis with passive congestion; acute congestion of spleen; passive congestion with fatty metamorphosis of liver; pseudo-hypertrophic muscular dystrophy.

Intestines scraped April 23, 12:30 p. m.; 200 c.c. 0.2 per cent. HCl used. Intestines thin but not anemic; small amount of mucosa relatively, much less than small dog; filtered quickly. No reactions were obtained with this preparation.

CASE 7.—May 1, 1907. Rather large fox terrier bitch. Dog fed on milk for five to six days; killed on morning of April 29, and put on ice. Dog quite thin and stomach and upper part of bowel filled with dark brown sawdust. At 3 p. m., April 30, four feet of bowel were cut out and put on ice. May 1, 3 p. m., worked up for secretin. Bowel pale and membrane came off rather less easily than usual, and made rather small amount; 150 c.c. 0.2 per cent. HCl required altogether; filtered quickly and clear at once.

CASE 8.—May 4, 1907. H. Z., male, white, age 21 years. Philadelphia Hospital. Died 9:15 p. m., May 3. Autopsy performed at 4:30 p. m., May 4. Pathologic Diagnosis: Hydropericardium; serofibrinous pleuritis; atelectasis and chronic pulmonary tuberculosis; chronic parenchymatous nephritis; slight fatty infiltration of liver; pneumo-thorax.

Body of a fairly well nourished man. Dark grumous material in lower bowel. Upper five feet of intestines look green-yellow as though from bile; tuberculous ulcer low in ileum (ten feet down or more), Peyer's patches swollen; 0.2 per cent. HCl used; six feet of intestine taken; made considerable bulk, more sand than usual needed; 300 c.c. HCl altogether; filtered with much difficulty and slowly; various filtrates used, and sterilized May 4, 8 p. m.

Above preparation active.

CASE 9.—E. F., male, black, age 40 years. Philadelphia Hospital. Died 6 p. m., May 6. Autopsy performed, 3:30 p. m., May 7. Pathologic Diagnosis: Brown atrophy of heart; edema and healed tuberculosis of lungs; slight chronic interstitial nephritis and parenchymatous nephritis; chronic passive congestion of spleen. Clinical Diagnosis (in part): Uremia or epilepsy.

Body well developed and nourished. Intestines worked up, 4 p. m., May 7: six feet used, 250 c.c. HCl, 0.2 per cent. Considerable scraping, which came off much more easily than usual. Small pieces of pancreas left on the back of bowel, possibly some scraped off too; filtered quickly and various filtrates and supernatant portions taken.

e. g., Supernatant plus HCl without anything else.
Supernatant plus HCl plus alkali and acid.

The latter was much more liquid than the former because the albumin coagulated and settled. Supernatant portions and those treated with alkali, etc., were filtered and finally some supernatant fractions were squeezed through muslin as usual and filtered. In working up this preparation it seemed to us most probable that it would be active, but it was not.

CASE 10.—K. F., female, white, age 52 years. Philadelphia Hospital. Died 12:30 a. m., May 18, 1907. Autopsy performed, 4:30 p. m. same day. Pathologic Diagnosis: Cloudy swelling of myocardium; dilatation of both ventricles; chronic passive congestion of spleen; cholelithiasis; general biliary pigmentation; hypertrophic cirrhosis of liver.

Body well developed. Six feet of bowel used; worked up, 3:30 p. m., May 19. Bowel membrane dark green, small amount of scraping which is watery and fluid; 75 c.c. of 0.2 per cent. HCl required, and mixture treated as usual. Rushed through without delay, and supernatant fluid as well as filtrate used.

This preparation was active.

CASE 11.—Calf. Intestines from abattoir. Animal several months old probably; membrane much like dog; bowel smaller; four feet of intestine and 120 c.c. 0.2 per cent. HCl used; unfiltered and filtered both taken; none squeezed through mesh. Membrane came off very easily, as does dog's, and made quite a little pile, though less than a large dog, as intestines are smaller, the size of a fountain pen.

CASE 12.—Sheep. Intestines from abattoir; smaller than calf, though animal (sheep) probably one year old. Scraped with greater difficulty and connective tissue came off with membrane, giving long strands in mortar; made a relatively small amount of scraping which did not seem to become digested by the 0.2 per cent. HCl, and made a gelatinous mass; 85 c.c. acid used. Supernatant fluid and filtrate both used.

CASE 13.—On May 21, 1907, a large puppy, setter type, was unsuccessfully operated on for a fistula and injected with secretin, and then the bowel removed and put on ice same day, about 6 p. m.

May 26, 3 p. m., bowel worked up. Membrane very loose and some loose material adherent to membrane, within bowel, apparently being cast off. No odor; in good condition; scraped easily, upper part more easily than usual; made considerable bulk; 125 c.c. 0.2 per cent. HCl used. All filtered, none squeezed through mesh.

CASE 14.—A. R., female, white, age 17 years. Philadelphia Hospital. Died 12:30 a. m., May 27, 1907. Autopsy performed 5 p. m. same day. Pathologic Diagnosis: General miliary tuberculosis; chronic parenchymatous nephritis; pneumonia; typhoid (?); fatty infiltration of liver.

Secretin worked up morning of May 28, and 0.4 per cent. acid used (4.1 c.c. of 1.2 sp. gr. HCl taken and diluted to 400 c.c. with H_2O); 75 c.c. acid required. Considerable bulk of membrane, which was thin, pink and scraped easily; filtered rapidly.

This preparation was unquestionably active.

CASE 15.—T. McK., male, white, age 50 years. Philadelphia Hospital. Died 7:40 a. m., June 16, 1907. Autopsy performed, 12 noon. Clinical Diagnosis: "Drink," erysipelas. Pathologic Diagnosis: Edema of lungs; acute vegetative endocarditis; cloudy swelling of myocardium; recent fibrous pleurisy; cloudy swelling of liver with fibrosis; acute diffuse splenic hyperplasia with multiple infarcts; acute parenchymatous nephritis.

Worked up, 1:30 p. m., same day. Abundant scrapings; bowel somewhat red and injected on scraping, but not before; considerable loose superficial mucoid material, as though there had been a catarrhal process. Scrapings made considerable bulk; six feet of intestine taken; 0.4 per cent. acid, only 65 c.c. used altogether; mixture was quite concentrated. Supernatant fluid was decanted and some filtered once only. The remainder not filtered at all.

This preparation was questionably active.

CASE 16.—June 18, 1907. Intestine of Irish terrier worked up; operation for fistula to-day failed; considerable scrapings; 150 c.c. 0.4 per cent. acid used; all filtered.

Observations on the levels reached by the pancreatic juice as it flowed in the canula, before and after injection of secretin. Markings are ⅛ inch apart. Canula about ⅛ inch in diameter.

APRIL 2, 1907.—SMALL FOX TERRIER. CANULA USED HERE CONTAINS FIFTEEN DIVISIONS.

At 3:34 p. m. at No. 6. Count from 0. Had been between 5 and 6 for several minutes; flowing pretty steadily after original spurt until within past ten minutes.

3:37, still at 6.

3:40, at 8.

3:42, at 9.

3:44, at 14.

25 c.c. HCl thrown in duodenum at 3:37; at 3:40 juice in canula sucked out by means of fine glass tube.

3:47, at 3¼.

3:48, going slowly.

3:51, nearly 5 (nearly 9 from outer end).

3:52, going slowly now.

3:53, still hardly reached 9 from outer end.

4:00, still at 9.

Secretin, (Case 2, J. C.) thrown in, 4 c.c.

4:06, has just passed 9.

4:08½, has not moved.

4:11, at 8½.

10 c.c. (Case 2, J. C.) thrown in at 4:11 (left leg vein).

4:13, no movement.

10 c.c. more injected (4:13).

4:15, moving apparently at normal rate, very slowly, has not touched 8.

4:20, barely at 8.

4:21, 25 c.c. HC. thrown in duodenum.
4:25, has moved and left 8.
4:27, at 7½, evidently moving, but rather slowly.
4:28, apparently stopping at 7½ from far end.
4:29, at 6.
4:30, at 5.
4:30½, at 4.
4:31, at 2.
4:32, at 1.
4:33, at 0, tube filled.
4:33½, emptied to 10 from outer end.
4:35, not quite to 9.
4:36, apparently stopping just short of 9.
4:39, stopped at 9.
4:43, stopped at 9.

Apparently a very faint reaction to HCl in bowel, probably because of clot, but none to secretin.

APRIL 6, 1907.—FOX TERRIER DOG, OPERATED ON.

3:11, tube nearly filled: juice hardly moving.
3:16, 8½ from outer end.
3:22, at 8¼.

About 3 c.c. dog secretin (Case 3) thrown in, about 3:25.

3:30, at 8.
3:33, at 2.
3:35, filled up.
3:36, sucked out to 11; tube filled with air bubbles and effort to remove them consumed some moments.
3:39, movement apparently over.
3:39½, at 9 ½.
3:41, at 8, moving still, but moves slowly.
3:43, nearly at 7. First big jump was made in about 2 minutes.
3:45, at 7½.
3:47, nearly at 6.
3:50, just at 6.
3:51½, at 5½.
3:54, at 5½.
3:56, at 5¼.

Amounts were thrown in; were hard to estimate, but the syringe held 10 c.c. Much of it escaped behind the plunger, though a few c.c. could be seen going into vein.

4:01, at 4.
4:04, at 3¼.
4:05, at 3.

A few minutes after first injection another was made, time not noted in confusion, but about 3:30; a marked reaction followed first injection, promptly, violently, and about the same time the other (second) injection was given.

4:10, at 2. Moving quite uniformly, though not nearly so rapidly as at height of activity.
4:13½, at 1.
4:17½, tube filled, zero.
4:18, emptied to 11.

Some secretin (Case 3) thrown in at 4:21.

4:21, at 9½.
4:22, barely at 9.
4:24, at 8¾.
4:25, at 8½.
4:26, moving faster than it has for some minutes, at 8 now.
4:27½, has passed 8.
4:29, at 7½.
4:31½, at 6¾.
4:33½, at 6 2/5.
4:35, at 6.
4:38, at 5¼.
4:39½, at 4 4/5.
4:45, emptied to 10¾.
4:45½, nearly 10.
4:46½, at 10.
4:47, at 9¾. Same rate of flow as before; 10 c.c. thrown in.
4:48, at 9 1/5.
4:49, at 8.
4:49½, at 7.
4:50½, at 6.
4:51, at 4¾.
4:51½, at 4.
4:52, at 1. Slight coughing.
4:52½, tube filled.
4:53½, sucked out to 10.
4:54, at 9.
4:54½, at 8.
4:55, at 7.
4:56, apparently going a little slower, at 6⅛.

4:56½, at 5 3/5.
4:57½, at 5.
4:59, at 4.
5:01½, at 3.
5:04, at 2.
5:09, tube filled.
5:10, sucked out to 11.
5:11½, at 10.
5:12, 25 c.c., 0.2 per cent. HCl thrown into duodenum.
5:13½, at 9.
5:14½, at 8, moving visibly faster.
5:14¾, at 6.
5:15, at 4; 2 divisions in 15 seconds; tube overflows at 5:15½.
5:16½, sucked out to 8. Flowing faster than ever yet seen.
5:17, tube filled. Dog struggling somewhat from lack of ether.
5:18½, at 2.
5:18¾, at 1.
5:19—at 0, full.

Sucked out and count made from proximal end.
5:19½, at 0.
5:19½, at 1.
10 seconds later, at 2.
5 seconds later, at 3.
5 seconds later, at 4.
5 seconds later, at 5.
5 seconds later, at 6.
8 seconds later at 7.
5 seconds later, at 8.
5 seconds later, at 9.
Filled up.
5:21½, at 0.
5 seconds later, at 1.
5 seconds later, at 2.
8 seconds later, at 3.
10 seconds later, at 4.
10 seconds later, at 5.
18 seconds between next mark, getting slower.
Dog killed, at 4:25.

Results marked. Second injection did not enter veins as they were blocked up. Third injection of secretin was made into left leg by a new opening and new syringe; all went in, 5 c.c.. Reaction most violent to the HCl in duodenum; went so fast as to be uncountable, even when called out by a watcher.

(Dog secretin successful; none other tried.)

APRIL 17, 1907.—COCKER SPANIEL, MEDIUM SIZED; TUBE INTRODUCED INTO AN OPENING IN THE PANCREATIC DUCT, OUTSIDE OF GUT.

4:38, at 6 from outer end.
4:38½, at 5.
4:39, at 4.
4:39½, at 3.
4:40¼, at 2.
4:41, at 1.
4:41½, at 0.
Sucked out to 10.
4:42½ at 9 from outer end.
4:43 at 8.
4:44, at 7.
4:45′ 10″, at 6.
4:46′ 50″, at 5.
Going slower, but moving constantly.
4:48′ 20″, at 4 from outer end.
4:50½, at 3.
Considerably slowed.
4:53′ 45″, at 2 from outer end, much slower.
4:58′ 30″, at 1¼.
Sucked out to 10½.
5:00′ 30″, at 10 from outer end.
5:02′ 15″, just barely passed 10, going extremely slowly.
4.5 c.c. secretin (Case 4, McM.) thrown in at 5:02′ 30″, into vein of leg.
5:07, moving very slowly, at 9½.
5:09′ 30″, moved slightly, nearly at 9.
5:12′ 30″, at 9 from outer end.
5:15, nearly past 9.
5:21′ 45″, at 8½.
5 c.c. secretin (Case 4, McM.) thrown in at 5:22′ 30″; 5:25 at 8½ from outer end; 5 c.c. more thrown in.
5:30, moving, but slowly.
5:35, has barely reached 8.
5:40, has barely passed 8.
5 c.c. dog secretin thrown into vein of leg, at 5:41.
5:43 at 8.
5:45, at 8.
5:50, at 7¾ from outer end.

5:54, at 7¼, barely.
5:54, 5 c.c. dog secretin (Case 5) thrown in.
5:55, 5 c.c. more new dog secretin thrown in.
5:58, bile in large quantities oozing out; big clot in canula.
6:02, moving fast, too fast to count; went 7 divisions in about 1 minute.
6:04, at 2 from end.
6:05, quieting down, but moving.
6:05, tube full.
6:05, sucked out to 7½.
6:07, at 7 from outer end.
6:07½, at 6½.
6:08′ 20″, at 4.
6:08′ 20″, at 3.
6:08′ 50″, at 2.
6:09′ 30″, at 1.
6:10′ 30″, nearly full, sucked out to 17.
6:14½, at 14.
6:16, at 9⅔ from outer end.
6:16′ 30″, at 9.
6:17½, at 8.
6:18½, at 7.
6:20, at 6.
6:21¾, at 6.
Secretion at bottom of tube at 6:32½.
5 c.c. human secretin thrown in then.
5 c.c. more human secretin thrown in at 6:33½.
6:42, bile flowing furiously through canula introduced into common bile duct.

In the light of later experiments, clots in canula evidently prevented good action, but the dog secretins seemed to cause a reaction.

No conclusions based on such responses as the above, however.

April 18, 1907.—Small Fox Terrier.

3:08½, at 3½ from outer end.
3:09, at 6.
3:09′ 50″, at 10.
3:10′ 12″, at 11.
3:11, at 12½.
3:11′ 20″, at 13.
3:12, at 14.
3:12′ 50″, at 15.
5 c.c. dog secretin (Case 5), at 3:14; going slowly at 3:14.
3:14′ 30″, at 16.
3:15, moving faster.
3:15′ 30″, at 18.
3:15′ 45″, at 19, marked response.
3:16′, at 20, marked response.
3:16′ 16″, at 21, marked response.
3:16′ 30″, at 22.
3:16′ 42″, at 23.
3:17, at 24.
3:17′ 15″, at 25.
3:17′ 43″, at 26.
3:18′ 30″, at 27; slower.
3:19′ 10″, at 28.
3:19′ 57″, at 29.
3:21′ 45″, at 30.
Sucked out to 25 at 3:22; moving slowly at 2:23′ 30″.
3:24, just over 25.
5 c.c. human secretin (Case 4, McM.) thrown in at 3:24.
3:24′ 23″, at 26.
3:25, at 27.
3:26′ 08″, at 28.
3:26′ 50″, at 29 (sucked on).
3:27′ 50″, at 30.
Sucked out to 24½, at 3:28′ 30″.
3:30′ 30″, at 25.
5 c.c. new dog secretin (Case 5) thrown in at 3:30′ 45″.
3:31′30″, at 26.
3:32′ 40″, at 27.
3:32′ 50″, at 28 (fast).
3:33′ 08″, at 29.
3:33′ 25″, at 30.
3:33′ 50″, at 31.
3:34′ 16″, at 32.
3:34′ 40″, at 33.
3:35′ 08″, at 34, slower.
3:35′ 38″, at 35.
3:36′ 08″, at 36, slowing to normal.
3:37′ 16″, at 37.
3:38′ 30″, at 38.
Sucked out to 25, at 3:39.
3:39′ 50″, at 25½.
5 c.c. dog secretin (Case 3) thrown in at 3:40.
3:40′ 30″, at 27.
3:40′ 50″, at 28, fair response.

Blood in bottom of canula.

3:41′ 10″, at 29, fair response.
3:41′ 43″, at 31, fair response.
3:42′, at 32.
3:42′ 20″, at 33.
3:42′ 42″, at 34.
3:42′ 10″, at 35.
3:43′ 40″, at 36, slower.
3:44′ 18″, at 37, much slower.
3:44′ 52″, at 38.
3:46′ 05″, at 39, very slow.
Sucked out to 24.
3:49′ 00″, at 24.
3:50′ 15″, at 24⅓.
3:50′ 30″, at 25.
5 c.c. human secretin (Case 4) at 3:50′ 45″.
5 c.c. more human secretin (Case 4) at 3:51′ 30″.
3:51′ 52″, at 26.
3:52′ 40″, at 27.
3:53′ 50″, at 28, slow, apparently stopped.
3:57′ 30″, at 28½, hardly moving; sucked out to below lowest gradation.
About 2 divisions below at 4 p. m.
Moved about ½ division at 4:02 p. m.
5 c.c. dog secretin (Case 5) at 4:02′ 30″.
5 c.c. more (Case 5) at 4:03′ 20″.
4:03′ 30″, at 1, fast.
4:03′ 50″, at 2, fast.
4:04′ 05″, at 3, fast.
4:04′ 08″, at 4, fast.
4:04′ 15″, at 5, fast.
4:04′ 20″, at 6, fast.
4:04′ 25″, at 7, fast.
4:04″ 30″, at 8, fast.
4:04′ 38″, at 9.
4:04′ 45″, at 10.
4:04′ 48″, at 11.
4:04′ 53″, at 12.
4:06′ 00″, at 13.
4:06′ 10″, at 14.
4:06′ 15″, at 15.
4:06′ 20″, at 16.
4:06′ 25″, at 17.
4:06′ 32″, at 18.
4:06′ 38″, at 19.
4:06′ 47″, at 20.
4:06′ 54″, at 21.
4:07′, at 22.
4:07′ 07″, at 23.
4:07′ 19″, at 24.
4:07′ 25″, at 25.
4:07′ 37″, at 26.
4:07′ 48″, at 27.
4:07′ 58″, at 28.
4:08′ 10″, at 29.
4:08′ 28″, at 30.
4:08′ 40″, at 31.
4:08′ 51″, at 32.
4:09, at 33 (dog moved).
4:09′ 07″, at 34.
4:09′ 18″, at 35.
4:09′ 27″, at 36.
4:09′ 36″, at 37.
4:09′ 47″, at 38.
4:10′, at 39, full up.
Sucked out to 0, at 4:10′ 30″.
4:11′ 10″, at 3.
Pencil dropped.
4:11′ 30″, at 5.
4:11′ 45″, at 6.
4:12′, at 7.
4:12′ 18″, at 8.
4:12′ 34″, at 9.
4:12′ 55″, at 10.
4:13′ 12″, at 11.
4:13′ 37″, at 12.
4:13′ 53″, at 13.
4:14′ 25″, at 14.
4:14′ 50″, at 15.
4:15′ 13″, at 16.
4:15′ 44″, at 17, slowing down.
4:16′ 20″, at 18.
4:16′ 57″, at 19.
4:17′ 55″, at 20.
4:18′ 48″, at 21.
4:19′ 45″, at 22 (normal rate).
4:21′ 25″, at 23.
Bile duct now exposed, 4:22; canula put in duct.
4:30, flow of bile almost stationary in tube.
4:32′ 20″, 5 c.c. human secretin thrown in.
4:33′ 30″, bile moving very slightly.
4:34, faster (?).
4:37, pancreatic flow not changed.
4:38, apparently slower flow of bile (no marks on tube in bile duct).
4:39, new dog (Case 5) thrown in.
4:40, pancreatic juice stationary at 29.
5 c.c. more secretin at 4:40′ 30″.

Little or no result from human secretin on bile; none on pancreas.
4:41′ 30″, sucked out; pancreas started to flow slightly; 3 divisions.
Pancreas started up, rapidly moving; as before, too fast to put down.
10 divisions to 30 seconds, at 4:43′ 30″.
Stomach contents furiously pouring out at 4:43.
Pancreas, 3½ divisions in 30 seconds.
4:45 p. m., slower, no evident effect on bile in canula.
4:50, dog killed.

APRIL 27, 1907.—FAIRLY LARGE WOOLLY DOG.

No movement at 12 noon, at mark 3.
No movement at 12:01′ 20″.
Very old dog secretin (Case 3) thrown in, 12:10, with no result.
12:33′ 30″, HCl introduced into bowel, juice stands at 1.
12:38, no movement.
12:41, at 2, hardly moved at all.
12:43, at 2½, just barely moving.
12:51, barely moving, after sucking, etc.; now at 9¾.
12:53′ 30″, at 10, peristalsis active.
12:56, at 10.
12:57′ 30″, at 10½.
1:03, barely moving.
1:03′ 30″, 5 c.c. new dog secretin (Case 5).
Fluid bloody since start.
1:10, hardly at 11.
1:15, dog killed.

Gall bladder not over full; little bile in guts; no food except in rectum.
No response; evidently due to invisible clots or some undetermined factor.

APRIL 28, 1907.—SMALL BITCH, SIZE OF FOX TERRIER.

Duct opened instead of gut; canula directly in duct.
Juice clean and runs freely at once.
Ran to 19, and then slowed down at 11:47.
11:50′ 30″, at 23.
11:51, at 24.
11:52, at 25.
11:52′ 10″, at 26.
11:52′ 45″, at 27.
12:02, sucked out to 0.
12:03, 4 c.c. new dog secretin (Case 5) injected, right thigh.
Level constant, practically at 0.
16 divisions to ½ minute at 12:03′ 50″.
Too fast to count, reaction in less than 45 seconds.
Full up at 12:04′ 45″.
12:04′ 45″, at 35.
Sucked out to 0, at 12:06.
12:06′ 20″, at 10.
12:06′ 50″, at 20.
12:07′ 08″, at 25.
12:07′ 30″, at 30.
12:08, at 35.
Sucked out to 0.
12:09′ 08″, at 5, slower.
12:09′ 50″, at 10.
12:10′ 55″, at 15.
12:12′ 20″, at 20, slower.
12:14′ 40″, at 23, very slow.
Sucked out to 0, at 12:15.
12:16′ 05″, at 1.
5 c.c. secretin (Case 6, E. B.), at 12:17.
12:19, no movement.
12:20, at 3.
12:21′ 40″, at 4.
12:23′ 30″, at 5.
5 c.c. old dog secretin (Case 3) at 12:24′ 30″.
First movement at 12:25.
12:25′ 10″, fast.
12:25′ 40″, at 20.
12:26′ 03″, at 25.
12:26′ 40″, at 30.
12:27′ 08″, at 35.
Sucked out to 0 at 12:27′ 30″.
Slowing.
12:29′ 50″, at 5, slowing.
12:30′ 40″, at 6, slowing.
12:31′ 15″, at 7, slowing.
Almost normal rate now.
12:32, at 9.

12:32′ 15″, 5 c.c. secretin (Case 6, E. B.) thrown in.
12:33, at 10.
12:34, at 11.
12:35′ 20″, at 12.
12:36′ 30″, at 13.
12:37′ 20″, at 14.
12:38′, at 15.
12:39′ 30″, at 16.
12:40′ 45″, at 17.
12:42′ 05″, at 18.
Sucked out to 0, at 12:42′ 45″.
12:43′ 20″, 5 c.c. new dog secretin (Case 5).
12:43′ 55″, first slight movement.
12:44′ 20″, at 5.
12:44′ 30″, at 10.
12:45′, at 20.
12:45′ 29″, at 25.
12:46′ 45″, about full.
Good marked reaction, but not so violent, though just as prompt as first new dog.
12:51′ 30″, at 4½.
5 c.c. 0.2 per cent. HCl injected into vein at 12:51′ 40″.
12:52′ 40″, at 6.
No movement.
12:55′ 25″, at 7.
Dog killed.

Almost nothing in the small intestines, except bile; a few stray strands of yellow feces, a few hard feces in rectum; considerable bile in gut. Gall bladder not so filled as in dog of April 27, 1907.

May 2, 1907.—Small Brown Terrier, Well Nourished.

4:55′ 45″, at 10½.
4:57, at 11½.
4:58, at 12.
5:00, at 13¼, pretty constant and slow.
5:01′ 40″, at 14.
5:04′ 30″, at 15.
Starting anew, flow constant and slow, 5 c.c. newest dog secretin (Case 7) left leg, at 5:05′ 15″.
Flow started at 5:06.
Going very fast at 5:06′ 10″.
Full at 5:07.
Sucked out to 0 at 5:07′ 15″.
5:07′ 30″, at 5.
5:07′ 50″, at 10, slower.
5:08′ 20″, at 15.
5:08′ 55″, at 20.
5:09′ 45″, at 25.
5:11, at 30.
5:14′ 30″, slow, and 5 c.c. secretin (Case 6, E. B.) thrown in.
5:14′ 45′, at 2.
No movement at 5:17; no reaction.
No movement at 5:18′ 30″.
No movement at 5:19′ 30″, only normal rate, very slow; no reaction five minutes later.
5 c.c. very old dog secretin (Case 3) thrown in, 5:19′ 50″.
5:20, at 4.
First movement at 5:20′ 07″.
5:20′ 54″, at 20.
5:21′ 20″, at 25.
Marked reaction.
5:21′ 37″, at 30.
5:21′ 52″, at 35, slower.
Sucked out to 0.
5:22′ 24″, at 5.
5:23′, at 10.
Much slower now.
5:23′ 35″, at 15.
5:26, slowed to almost normal.
5:26′ 50″, at 20.

May 5, 1907.—Small Black Bitch.

12:39′ 35″, juice at 0, and 5 c.c. Case 3 (very old dog) secretin thrown in.
Barely moving.
12:40′ 33″, first movement.
12:41′ 07″, at 5
12:41′ 53″, at 10
12:42′ 30″, at 15
} Not so fast as usual; a small clot visible in tube; moving on.
Very slow.
12:45′ 20″, at 16.
12:46′, 5 c.c. very old dog secretin (Case 3) different flask, thrown in.
12:46′ 20″, at 16½.
First movement at 12:47′ 28″.
12:48′ 42″, at 20.
Very slow, but evidently accelerated.
12:49′ 21″, at 21.

12:50′, at 22.
12:50′ 30″, at 23.
12:51′ 03″, at 24.
12:51′ 27″, at 25.
12:52′ 15″, at 26.
12:54′ 20″, at 27½.
Sucked out to 5.
12:55′ 30″, at 5, not moving.
12:56′ 10″, 10 c.c. human secretin (H. Z., Case 8) thrown in, right hind leg.
12:58′ 10″, at 6.
1:00′, at 7.
No movement.
1:04′, at 8.
Not moving visibly.
10 c.c. old dog secretin of a dilution of 1 to 4 (2 c.c. secretin, 8 c.c. H_2O, distilled) thrown in then.
1:11′ 30″, at 9 1/5.
No movement.
10 c.c. dilution of 1 to 1 (5 c.c. secretin, old dog) to 5 c.c. distilled water, thrown in at 1:14′ 45″.
1:14′ 30″, at 9 1/5.
First movement at 1:16′ 30″.
1:16′ 45″, at 10.
1:17′ 20″, at 11.
1:18′ 15″, at 12.
1:18′ 57″, at 13.
1:19′ 40″, at 14.
1:20′ 15″, at 15.
1:21′ 45″, at 16.
1:22′ 50″, at 18.
1:24′ 10″, at 19.
1:25′ 20″, at 20.
1:26′ 50″, at 21.
1:30′ 45″, at 22½.
5 c.c. very old dog secretin, first flask, thrown in at 1:31′ 25″.
1:32′ 40″, at 23.
1:33′ 10″, moved visibly, very slightly.
1:34′ 10″, at 24.
1:34′ 50″, at 25.
1:35′ 15″, at 26.
1:35′ 30, at 27.
1:35′ 50″, at 28.
1:36′ 16″, at 29.
1:37′ 10″, at 30 (irregular meniscus).
1:37′ 40″, at 31.
1:38′ 35″, at 32.
1:39, at 33.
Sucked out to 3.
1:39′ 45″, at 3.
1:40′ 15″, at 4.
1:42′ 05″, at 5.
1:43′ 15″, at 6.
1:47′ 15″, at 7, nearly.
10 c.c. (Case 8, H. Z.) thrown in at 1:47′ 48″.
1:49′ 07″, at 7.
1:50′ 30″, at 8.
1:50′ 50″, at 9.
1:51′ 15″, at 10.
1:52′ 15″, at 11 almost (upper meniscus).
1:52′ 35″, at 11.
1:53′ 03″, at 12.
1:53′ 30″, at 13.
1:54′ 40″, at 14.
1:56′ 25″, at 14½.
1:57′ 30″, not yet 15.
5 c.c. secretin (Case 8, H. Z.) thrown in at 1:57′ 50″.
5 c.c. more secretin (Case 8, H. Z.) thrown in at 1:59′ 10″.
1:59′ 20″, at 18.
1:59′ 40″, at 19.
2:00′ 18″, at 20.
2:01′ 10″, at 21.
2:01′ 50″, at 22.
2:02′ 45″, at 23.
2:04′ 50″, at 24.

Two distinct responses, of the human, equal or almost equal to the dog. Reaction of dog to all stimuli very slight, relatively, to most dogs tried so far; the reaction was slow to set in and seemed to gather speed slowly and to last longer proportionately for the speed, though, perhaps, the delayed response accounted for that.

Slight amount of yellowish fluid in upper part of gut and slight amount of dark green feces throughout bowel, but practically nothing of consequence.

MAY 8, 1907.—SECRETIN. IRISH TERRIER, FAIRLY GOOD SIZE. CANULA IN DUCT, NOT IN GUT.

2:01′ 10″, at 5.
2:02′ 05″, at 10.
2:03′ 13″, at 15.
2:07′ 30″, at 20.
Going much slower after the usual initial spurt.
Sucked out to 0 at 2:12′ 50″.
2:10′ 30″, practically stopped, hardly at 1.
2:13′ 45″, at 1 (hardly there).
2:14′ 10″, 5 c.c. (Case 7) newest dog secretin in right thigh.
First movement at 2:15′ 20″.
2:16′ 10″, at 2, very slow.
2:17′ 40″, at 3, very slow.
Very atypical response.
2:20′ 30″, at 3 (practically stopped).
2:20′ 40″, 10 c.c. (Case 7) newest dog.
2:22′ 30″, started.
2:22′ 35″, at 5, response better than last, but slow.
2:22′ 50″, at 6, response better than last, but slow.
2:23′ 58, at 8.
2:25′ 25″, at 9.
Slowing down much.
2:40′ 45″, at 11½.
2:43′ 15″, at 12.
10 c.c. secretin (Case 8, H. Z.) at 2:43′ 15″.
No response, same flask as last time.
10 c.c. (Case 3) very old dog, at 2:51′ 50″.
A response from this, faster than before, but not fast. However, tube filled up.
Sucked out to zero.
2:59, at 0.
10 c.c. secretin (Case 9, E. F.) at 2:59′ 30″.
Moving at same rate at 3:00′ 30″.
Clot in canula, apparently of juice chiefly.

SECOND DOG.—SMALL FOX TERRIER BITCH.

5 c.c. (Case 8) newest dog secretin, at 3:33. Juice at bottom of canula.
Response at 3:34.
Going fast at 3:34′ 45″.
3:35′ 05″, at 5.
3:35′ 30″, at 7.
3:35′ 42″, at 8.
3:36′ 09″, at 9.
3:37′ 22″, at 10.
3:37′ 36″, at 11.
3:37′ 40″, at 12.
3:37′ 52″, at 13.
3:38′ 08″, at 14.
3:38′ 53″, at 15.
3:39′ 10″, at 16.
Slower.
Sucked out to 0, at 3:40.
Good response.
3:41′ 25″, at 1.
3:42′ 30″, at 1 1/5.
10 c.c. (Case 9, E. F.) secretin at 3:42′ 55″.
No response.
Clogged up, large red clot in tube and vessels.
Pancreas seems sclerosed.

MAY 9, 1907.—FOX TERRIER BITCH, THIN AND RATHER SMALL.

2:15′ 50″, at 0.
2:16′ 20″, at 1.
2:17′ 45″, at 2.
Very little initial spurt.
2:21′ 30″, at 2.
5 c.c. newest dog (Case 7) secretin at 2:21′ 45″.
First movement at 2:22′ 25″.
2:22′ 30″, at 5.
2:22′ 39″, at 10.
2:22′ 50″, at 15, too fast to count and jot down.
2:22′ 55″, at 20, too fast to count and jot down.
2:23′ 00″, at 30, too fast to count and jot down.
Sucked out to 3.
2:23′ 25″, at 5.
2:23′ 40″, at 10.
2:24′ 00″, at 15, slower.

2:24′ 32″, at 20.
2:25′ 05″, at 25.
2:26′ 38″, at 29.
2:27′ 26″, at 30, about normal rate.
Sucked out to 3.
2:30, at 3½.
10 c.c. secretin (Case 7, H. Z.) at 3:30′ 20″.
First movement at 2:31.
2:31′ 04″, at 5.
2:31′ 45″, at 10.
2:32′ 25″, at 12½.
2:32′ 40″, at 13.
2:33′ 07″, at 14.
2:34′ 10″, at 15.
2:35′ 38″, at 16.
10 c.c. secretin (Case 9, E. F.) first unfiltered, supernatant, at 2:36′ 20″.
2:38′ 10″, at 17, same rate.
No response. Result of both injections clear.
First tuberculous case (H. Z.) gave a distinct response, slower than dog and apparently not quite so soon (though see figures).
2:44′ 30″, at 18 (constant).
10 c.c. secretin (Case 9, E. F.), treated with both HCl and alkali, etc.
2:47′ 25″, first movement.
2:48′ 48″, at 19, no response.
2:49′ 52″, at 20, no response.
2:53′ 40″, at 21 (nearly) no resp.
10 c.c. newest dog secretin (Case 7) again at 2:54′ 34″.
First movement, at 2:55′ 25″.
2:55′ 38″, at 25.
2:55′ 48″, at 30.
2:55′ 53″, at 35.
Lost; too fast to count.
2:56′ 10″, at 10.
2:56′ 18″, at 15.
2:56′ 26″, at 20.
2.56′ 34″, at 25.
2:56′ 45″, at 30.
2:56′ 57″, at 35.
Sucked out to 3.
2:57′ 12″, at 5.
2:57′ 52″, at 10, slower.
3:02′ 45″, at 12.
10 c.c. (Case 9, E. F.) squeezed and filtered, at 3:03′ 20″.
3:06′ 25″, at 13, no response.
3:09′ 00″, at 13½.
10 c.c. secretin (Case 8, H. Z.) late filtrate, injected at 3:11′ 30″.
At time of injection, juice not moved from 13½.
First movement at about 3:13′ 40″.
3:13′ 10″, at 15.
3:13′ 48″, at 16.
3:15′ 04″, at 17.
Slight response, less than the other from same case, but distinct.
3:17′ 25″, 10 c.c. secretin (Case 8) earlier than last, but perhaps later filtrate than that first injected.
3:19′ 15″, at 18.
3:24′ 55″, at 19, no response.
10 c.c. secretin of (Case 9, E. F.) later filtrate, over night, at 3:26′35″.
3:28′ 00″, at 19½; no response.
10 c.c. very old dog secretin (Case 3) at 3:29′ 35″.
First movement at 3:30′ 35″.
3:30′ 58″, at 20, active; preparation must be some 5 or more weeks old.
3:31′ 13″, at 30.
Sucked out to 3.
3:31′ 38″, at 5.
3:32′ 07″, at 10.
3:32′ 55″, at 13½.
3:34′ 00″, at 16, slowed down.
3:35′ 03″, at 17.
10 c.c. of a solution made up of HCl, NaOH and CH_3COOH in the proportions used in making secretin extracts, was injected at 3:35′ 40″.
No response.
3:46′, at 19.
10 c.c. most active flask of (Case 8, H. Z.) heavy precipitate, at 3:47′ 10″.
First movement, at 3:48′ 55″.
3:50′ 20″, at 20.
3:54′ 15″, at 21.
Very slow response, if any, probably the slightest possible.
3:56′ 15″, at 21½.
10 c.c. (Case 8) much alkali and acid, at 3:56′ 47″.
3:59′ 10″, at 23.
4:00′ 45″, at 24.
A response, but not great. Curiously, the preparation first used just before this did not act, when it did earlier in the day.
4:04′, at 25.

10 c.c. newest dog (Case 7) secretin at 4:04′ 15″.
Tube sucked out to 4½.
First movement at 4:06′ 28″.
4:06′ 29″, at 5.
4:06′ 50″, at 7.
4:07′ 05″, at 8.
4:07′ 20″, at 9.
4:07′ 33″, at 10.
4:07′ 58″, at 11.
4:08′ 50″, at 12.

Distinct response, but not so marked as before. Does the general condition of the dog account for it? At one time she nearly died from too much ether. Canula worked beautifully to-day and no clot in end.

None of the E. F. (Case 9) preparations worked. Several of Case 8 preparations worked. None of the Case 9, E. F., preparations were put in Arnold sterilizer.

The preparation (Case 9) marked "much alkali and acid" was one carried somewhat beyond neutrality, and then brought back to relatively strong acidity to get out all possible proteid. It worked.

Stomach full of well digested fluid and food. Upper part of intestine contains some light yellow food, then becomes pretty free and further down contents are fecal in nature and pretty profuse. Bowel therefore much fuller than with recent dogs. (Last two not examined, but not fed beforehand; this one was, at 10:45 a. m.)

MAY 21, 1907.—(1) SMALL FOX TERRIER.

A failure, as canula would not go in and tissues became too bruised and torn to be of any use.

(2) LARGE PUPPY, SETTER TYPE.

4:30, at ¾.
4:30′ 25″, at 1.
4:31′ 10″, at 2. Divisions are ¼ inch instead of ⅛ inch.
4:32′ 30′, at 3, usual initial flow followed by decrease.
4:37′ 30″, very slow.
4:38′, barely at 4.
5 c.c. dog secretin of April 17 (Case 5) at 4:39′ 30″.
Not yet 4.

Both failures, mechanically. Pancreatic duct of second dog branched so early that the common duct was too short to allow of satisfactory tying in the canula. In both dogs the canulæ were introduced outside of bowel; bowel not opened.

MAY 22, 1907.—FOX TERRIER BITCH.

Juice flowing fast when canula first put in. Marks on canula about ¾ apart.
3:00 p. m., at ¾.
3:01′ 30″, at 1.
5 c.c. secretin Case 5 (dog of April 17) thrown in at 3:02′ 20″.
First movement, at 3:02′ 50″.
3:03′ 30″, at 3.
3:03′ 53″, at 4.
3:04′ 15″, at 5.
3:04′ 40″, at 6.
3:05′ 10″, at 7.
3:06′ 12″, at 8.
3:07′ 35″, at 9.
3:09′ 35″, at 10, much slowed down.
Sucked out to 2.
3:14′ 30″, at 2.
5 c.c. secretin (Case 10, K. W.) filtered.
3:15′ 00″, at 2¼.
3:18′ 30″, at 3, no response.
5 c.c. secretin (Case 10, K. W.) supernatant, at 3:19′ 50″.
3:22′ 45″, no response, juice at 3½.
3:24′ 30″, 5 c.c. same active dog secretin of April 17 (Case 5) thrown in.
3:27′ 30″, apparently no response, though canula sucks as though not blocked up.
3:28′ 30″, at 4.

3:34′ 50″, 10 c.c. dog secretin of April 17, (Case 5); level only at 4⅕.

Respiration affected.

3:36′ 20″, first movement.

3:36′ 35″, at 5.

3:37′ 15″, at 6.

3:38′ 25″, at 7 (slower, though a distinct response).

3:40′ 45″, at 8.

A thrombus in canula may have slowed flow. Also left leg vein may have thrombosed or injection may have been in artery. Last active injection made into right jugular.

3:44′ 30″, at 9.

10 c.c. calf secretin (Case 11) at 3:44′ 35″.

3:45′ 40″, first movement.

3:45′ 52″, at 10.

3:45′ 59″, at 11.

3:46′ 06″, at 12.

3:46′ 12″, at 13.

3:46′ 18″, at 14.

3:46′ 22″, at 15.

3:46′ 26″, at 16.

Juice now dropping into test tube to be saved for another purpose. The clot above mentioned was pushed out; juice viscid.

Sucked out to 2, at 3:49′ 10″.

3:50′ 05″, at 6; still very fast.

3:50′ 55″, at 7, slower.

3:53′, just over 8.

10 c.c. sheep secretin (Case 12) filtered and supernatant, at 3:53′ 15″.

3:54′ 05″, first movement.

3:54′ 10″, at 12.

3:54′ 20″, at 15.

Filled.

Violent reaction.

Sucked out.

3:55′ 13″, at 8, slower.

3:55′ 23″, at 9.

3:55′ 33″, at 10.

3:55′ 45″, at 11.

3:56′ 06″, at 12.

3:58′ 20″, at 16, full up.

Slowing, but violent response.

Sucked out, and at 4:04 has ceased flowing and stands at 2.

4:09′ 00″, at 2 1/6, hardly moved at all.

4:19′, at 2¼.

Sucked out to nearly 1.

10 c.c. calf secretin (Case 11) filtered, injected at 4:27′ 15″ to see if canula clear.

4:27′ 40″, response as before.

4:29′ 15″, at 3 (started at about 4:28′ 55″ or so).

4:29′ 43″, at 5.

4:29′ 57″, at 6.

4:30′ 12″, at 7, much slower than first.

4:30′ 30″, at 8, much slower than first.

4:30′ 43″, at 9.

4:30′ 54″, at 10, response.

4:31′ 10″, at 11, dog has been in poor shape for some time.

4:31′ 28″, at 12.

4:31′ 45″, at 13.

4:32′ 10″, at 14.

Slower.

4:33′ 08″, at 15, much slower.

10 c.c. sheep secretin (Case 12) supernatant, injected through gut wall into duodenum above pancreas at 4:38, and then 10 c.c. more.

4:37′ 30″, at 3 2/5, hardly moving.

4:38′ 45″, at 3 3/5.

4:40′ 30″, at 4.

4:48′, at 4¼, no response.

10 c.c. secretin (Case 10, K. W.) filtered and squeezed and filtered, injected into carotid.

4:49′ 15″, at 6.

4:49′ 23″, at 7.

4:49′ 30″, at 8.

4:49′ 50″, at 9, response.

4:50′ 05″, at 10.

4:50′ 29″, at 11.

4:51′, at 12.

4:52′ 20″, at 13.

4:54′ 20″, nearly 14.

4:55′, at 14 3/5.

Sucked out to 2⅕, almost constant.

10 c.c. supernatant secretion (Case 10, K. W.) at 4:58′ 30″ (dog nearly dead).

4:58′ 40″, started.

4:59′, at 6.

4:59′ 07″, at 7.

4:59′ 25″, at 9.

4:59′ 32″, at 10.

4:59′ 48″, at 11.

5:00′ 00″, at 12.

5:00′ 18″, at 13.

5:00′ 50″, at 14, slower.
Distinct response.
Sucked out to 2, at 5:05.
10 c.c. secretin (Case 4, McM.) at 5:05′ 50″, juice at 2¾ then.
5:06′ 20″, at 3.
Apparently no response.
10 c.c. calf secretin (Case 11) at 5:09′ 45″.
Response relatively mild.
Dog killed.

MAY 31, 1907.—SMALL MALE PUPPY, BULL TYPE.

12:47′ 10″, at 1 (marks ¼ inch apart).
12:50, at 2½, partly by sucking through fine tube introduced into canula.
Flowing very slowly.
5 c.c. secretin of Case 13 (setter dog kept on ice) at 12:52′ 50″, in right jugular.
12:53′ 15″, at 3.
Started in about twenty seconds or so.
12:53′ 48″, at 4.
12:53′ 57″, at 5, response.
12:54′ 10″, at 6.
12:54′ 24″, at 7.
12:54′ 42″, at 8.
12:55′ 08″, at 9.
12:57′, at 10, slow and possibly plugged up.
Small plug removed by making a "cork screw" out of catgut.
Sucked out to 9.
5 c.c. more secretin Case 13 put in, to wash out canula.
1:03′ 10″, 5 c.c. more secretin of Case 13.
1:04′ 08″, moved.
1:04′ 24″, at 14, too fast to count.
1:04′ 32″, at 15.
1:04′ 42″, at 16.
1:04′ 52″, at 17.
1:05′ 02″, at 18.
1:05′ 13″, at 19.
1:05′ 28″, at 20.
1:05′ 33″, at 21.
Full.
1:09, still moving.
Sucked out to 6.
5 c.c. secretin (Case 14, A. R.) young girl with tuberculosis, at 1:12′ 50″.
1:13′ 20″, at 7¼, practically stopped.
1:14′ 45″, at 7½, no response yet.
Trouble, canula out.
1:29′ 05″, 5 c.c. secretin (5-day-on-ice-dog) to clear tube.
Response, but canula evidently blocked.
5 c.c. more secretin (Case 13) at 1:34′ 30″, to clear duct.
More secretin Case 13; respiration affected, but it has not been much noticed to-day.
A slight sluggish response.
Canula seems clear yet movement atypical and not so good as at first.
5 c.c. more secretin (Case 13) again gave a slow response.
5 c.c. active calf secretin (Case 11) gave a slight movement, not sufficient to record (1 div.).
5 c.c. sheep secretin (Case 12) injected.
About 5 minutes later a quite marked flow, evidently a response.
5 c.c. more secretin of Case 13 (5-day-dog) gave a relatively slow but distinct response.
10 c.c. human secretin (Case 14, A. R.) cloudy, that is, but little filtered, at 2:21′ 45″.
Level at 3½, response in 35 seconds.
2:22′ 45″, at 5.
Cleansing wire taken out, level fell back.
2:23′ 05″, at 6.
2:23′ 35″, at 7, response.
2:24′ 15″, at 8.
2:25′ 15″, at 9.
10 c.c. clear secretin (Case 14, A. R.) young girl with tuberculosis.
2:29′ 15″, at 2.
2:30′ 33″, at 3.
2:31′ 15″, at 4.
2:31′ 56″, at 5.
2:32′ 45″, at 6, response.
On dissection, gland looked edematous under peritoneum; much alkaline pancreatic juice.

JUNE 18, 1907.—BROWN IRISH TERRIER.

Tried with secretin of Case 15 (McK.); canula about ⅝ inch in size, much larger, and fitted with platinum point.

No movement in tube, just a drop or so in bottom.

10 c.c. Case 15 (McK.) at 11:23.

Breathing changed at once.

Seemed to be a response from motion in canula, but injection used chiefly to start a free flow.

11:32′ 30″, flowing freely (marks ¼ inch apart).

11:34′ 20″, at 5.

11:37′, at 6 (slower, though moving).

11:41′ 20″, very nearly 7.

11:41′ 20″, 10 c.c. more of Case 15.

At 8, a clot in tube, clearly seen, long feathery and red.

The above apparently a response, but hardly dependable, as normal flow may have been very active.

JUNE 20, 1907.—LARGE BLACK DOG, SETTER TYPE.

11:15′ 35″, at 0.

11:16′ 05″, at 1.

11:17′ 25″, at 2½.

11:18′, at 3.

10 c.c. secretin Case 16 (dog of June 18) injected into carotid, at 11:18′ 40″.

11:19′, at 4.

First movement at 11:19′ 45″.

11:19′ 50″, at 7.

11:19′ 56″, at 8.

11:20′ 03″, at 9.

11:20′ 10″, at 12.

11:20′ 18″, at 15.

11:20′ 26″, at 19. } Too fast to
11:20′ 28″, at 20. } count, even
11:20′ 37″, at 25. } with biggest
11:20′ 43″, at 28. } tube.
11:20′ 48″, at 30. } Violent reaction
11:20′ 55″, at 32. }

11:21′, at 34.

11:21′ 06″, at 35.

11:21′ 16″, at 36.

11:21′ 27″, at 38.

11:21′ 43″, at 40.

Sucked out to 0, at 11:23′ 15″.

11:24′ 40″, at 1½.

11:25, at 2.

10 c.c. secretin Case 15 (McK.) injected into right jugular at 11:25′ 20″.

11:26′ 35″, at 3.

11:26′ 48″, at 4.

11:27′ 34″, at 5.

11:27′ 57″, at 6.

11:28′ 28″, at 7.

Response, but much less marked than that of dog.

10 c.c. more secretin of Case 16 (dog) tried, to obviate possibility of clot, at 11:30′ 35″.

Now slowed down.

11:30′ 45″, at 8.

11:31′ 40″, at 9.

11:31′ 50″, at 10.

11:31′ 58″, at 11.

11:32′ 03″, at 12.

11:32′ 08″, at 13.

11:32′ 13″, at 14.

11:32′ 17″, at 15.

11:32′ 22″, at 16.

11:32′ 28″, at 17.

11:32′ 32″, at 18.

11:32′ 38″, at 19.

11:32′ 43″, at 20.

11:32′ 49″, at 21.

11:32′ 53″, at 22 (lacteals show plainly in gut).

11:33, at 23.

11:33′ 07″, at 24.

11:33′ 15″, at 25.

11:33′ 28″, at 26.

11:33′ 58″, at 29.

Small clot somewhere, visible in material sucked out.

10 c.c. secretin Case 15 (McK.) unfiltered and simply decanted, at 11:38.

11:38′ 20″, at 3.

11:41′ 13″, at 4.

11:46′, at 5.

11:48′ 05″, at 6.

11:48′ 35″, at 15. } Marked response *very much delayed* and persistent when present.
11:49′ 15″, at 19.
11:49′ 40″, at 21.
11:50′ 15″, at 20.
11:50′ 25″, at 25. } Dog's heart action better than when human secretin was first thrown in this last time.
11:50′ 45″, at 26.
11:51′ 08″, at 27.
11:51′ 25″, at 28.
11:51′ 55″, at 29.
11:52′ 25″, at 30.
11:52′ 50″, at 31.
11:55′ 00″, at 32.
11:55′ 30″, at 35.

Cardiac depression perhaps a factor in slow response, but there was no cyanosis.

11:59′ 40″, at 1 (going very slowly).
12:03′ 45″, at 2.
12:05′, at 3.

10 c.c. secretin Case 15 (McK.) thrown in jugular vein at 12:06′ 05″.

12:06′ 37″, at 4.
12:07′ 40″, at 5.
12:08′ 40″, at 6.
12:09′ 35″, at 7.
12:11′, at 8.
12:14′ 45″, at 9½.

Even with accurate figures and timing, etc., it was very hard to tell whether the above human injection was a response or not. Certainly it was less than that of a dog, but possibly a response even so.

12:19′ 15″, at 10¾.
12:20′ 55″, at 11.

10 c.c. secretin Case 16 (dog of June 18) at 12:21′ 10″.

12:22′, at 12.
12:22′ 15″, at 13.
12:22′ 20″, at 14.
12:22′ 23″, at 15.
12:22′ 40″, at 20.
12:22′ 50″, at 25.
12:23′, at 30.
12:23′ 10″, at 35.
12:23′ 20″, at 40.
12:23′ 30″, at 45 (estimated).

Sucked out to 0.

12:23′ 57″, at 10.
12:24′ 07″, at 15.
12:24′ 15″, at 20.
12:24′ 20″, at 25.
12:24′ 40″, at 30.
12:24′ 55″, at 35.
12:25′ 09″, at 40.
12:25′ 24″, at 45 (estimated).
12:25′ 30″, at 0.
12:25′ 48″, at 5.
12:26′ 03″, at 10.
12:26′ 20″, at 15.
12:26′ 45″, at 20.
12:27′ 30″, at 25.

Dog breathing rapidly and respiration shallow, flow has slowed down considerably since last figures.

12:29′ 30″, at 30.
12:31, at 32.
12:33′ 30″, at 33.
12:36′ 20″, at 34.

10 c.c. secretin Case 15 (McK.) filtered, at 12:37′ 40″.

Sucked out.

12:38′ 15″, at 0.
Missed time at 1.
12:39′ 50″, at 2.
12:40′ 57″, at 3.
12:42′ 14″, at 4.
12:44′ 30″, at 5.

Seems to be a response, but vague like the last, and vastly below the dog preparations in efficiency.

THE PRESENT STATUS OF OUR KNOWLEDGE OF THE CHEMISTRY OF THE PROCESSES OF IMMUNITY.*

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It is extremely doubtful if, in the entire range of recent medical literature, there can be found a set of articles that contradict one another more flatly than do those that report the attempts so far made to learn something concerning the chemical nature and action of the substances concerned in the reactions of immunity. After contrasting one report with another, the product seems to be entirely neutral, or better, amphoteric, for one's conclusions will depend largely on one's choice of indicator. He may accept the word of the last disputant, or believe only the work of those whom he knows, or he may, with considerable propriety, be skeptical concerning most of the positive results and claims. Indeed, after a first review of the literature on this subject, the only hope seems to lie in the thought that "where there is so much smoke there must be some fire;" but if the work is arranged on a chronologic basis one gains courage by noting that the earlier hasty attempts that were made to explain everything in the chemistry of immunity on the basis of very limited experimental studies, are gradually being replaced by work that shows the intention, as expressed by Buxton and Teague,[1] "to collect data on which, in the future, sound theories can be built." Nevertheless, even in the most recent literature there is an abundance of ill-considered, immature speculation.

To illustrate by a typical example, in a publication of the current year it is recorded that one diphtheria antitoxin horse, which gave a very potent serum, gradually developed an increase in the globulin content of its blood, while another horse, that had a relatively abundant globulin content in its blood at the start, showed no increase in the globulin and little formation of antitoxin. On the basis of these two horses are proposed numerous theories to the effect that if a horse has normally a high globulin content in its blood it is unsuitable for the development of globulin antitoxin, that antitoxin formation is necessarily connected

* Presented in the Symposium on Immunity held by the Section of Physiology and Experimental Medicine of the American Association for the Advancement of Science, December, 1907.

1. Ztschr. physikal. Chem., 1907, lvii, 76.

with a globulin increase, etc., as if these two horses furnished conditions that would be duplicated by every other horse. Such articles impress on one the justice of A. E. Taylor's remark, that "in experimental pathology the results are in inverse proportion to the number of controls."

In the limited space available for the presentation of this subject it is impossible to attempt to develop the history of our knowledge, or lack of knowledge, of the chemistry of each of the phases of immunology; indeed, I can only attempt to sketch the present status of knowledge in certain fields as it appears to be of special interest at this time, for although there is as yet such a scant amount of positive information, there is no dearth of material in which to look for it.

Probably the fundamental question in the whole field of "immunochemistry" is the chemical nature of toxins, for until we know this we can only search in the dark for knowledge concerning the other, probably more complex, factors in the immunity reactions; yet at the present time there is absolutely nothing definite to be said concerning this subject. We have very good reasons for believing that the molecule of bacterial toxin is smaller than that of the typical proteins, or of the antitoxins, for toxins diffuse much more rapidly and pass more freely through dialyzing membranes, yet neither these facts, nor the facts that strong toxin solutions have been obtained which do not give the usual protein reactions, can be looked on as conclusive proof that toxins are not proteins.

To be sure, this view has received considerable credence, but it is by no means finally established. One of the main supports of the view that toxins are not proteins lies in the statements by Jacoby that the active constituent of ricin can be obtained free from protein; however, the careful studies of Osborne, Mendel and Harris[2] show that such a separation can not be made, for although they isolated the toxic substance in such purity that .001 of a milligram was fatal per kilo to rabbits, it still contained proteins. This work illustrates the reason for the failure of all our attempts to obtain the toxins, and the other substances participating in immunity reactions, in pure condition, viz., that they are so very potent that even the most active fluids with which we are familiar contain them in such minute quantities that they are far beyond the reach of chemical methods, especially as proteins and other complex substances are always present.

Take, for example, the cobra lecithid isolated by Kyes. Here is a most active compound of a toxin with a known chemical substance of

2. Amer. Jour. Physiol., 1905, xiv, 259.

fairly well-established composition and properties, which would seem to give us an opportunity to pin down a toxin for analysis; yet when the cobra lecithid is analyzed the figures for the elementary composition agree within the reasonable limits of analytic error with those for monostearyl lecithin alone.[3] In other words, an amount of the hemolytic constituent of cobra venom that is sufficient, when combined with lecithin, to destroy enormous quantities of red cells, is not sufficient in amount, in proportion to the amount of lecithin with which it is combined, to produce any appreciable modification of the analytical figures of the lecithin.

In view of these facts, the fatuity of much of the work that has been done in the attempt to localize the antitoxic constituent of horse serum must be apparent. Indeed, there are few phases of the subject of immuno-chemistry more full of contradiction than this one of the relations of the globulins to the antitoxins.[4, 5, 6] The amount of globulin in the blood, and the proportion of the total proteins of the blood that it constitutes, depend on too many factors to permit of their being brought into line with the antitoxin content. It has been found that feeding and starvation modify the globulin ratio of the blood, as do also infection and cachexia, and Bolognesi[7] believes that infecting bacteria may cause a direct change of serum albumin to a serum globulin. In general any change observed in the ratio of the blood proteins of experimental animals, whatever the cause may be, is either relatively or absolutely in favor of the globulins. Even in far less subtle problems than those of immunology, determinations of blood globulins have been found to be altogether unreliable. To illustrate: In the regeneration of the blood after hemorrhages Baumann[8] found that the albumin increases faster than the globulin, while other observers have found just the opposite relation. It is certain, therefore, that to attempt to correlate with the antitoxin production the proportion of globulin in an antitoxin horse which is suffering from repeated bleedings, local infections, systemic intoxication, and often also from general decrepitude and senility, is an impossible proposition.

This statement is not intended to reflect on the very valuable work that has been done in separating the antitoxin containing globulins of antitoxic sera from the other proteins. These studies have shown con-

3. Kyes: Biochem. Ztschr., 1907, iv, 99.
4. Glaessner: Ztschr. exper. Path. u. Ther., 1906, ii, 154.
5. Gibson: Jour. Biol. Chem., 1906, ii, 14; 1907, iii, 253.
6. Ledingham: Jour. of Hyg., 1907, vii, 65.
7. Biochem. Ztschr., 1907, vi, 149.
8. Jour. of Physiol., 1903, xxix, 18.

clusively that the antitoxin is actually bound in some way to the globulins, if it is not itself a globulin, for were its precipitation merely a mechanical dragging down, it would certainly come down with the proteins that are thrown out of the serum before the globulins begin to be precipitated. It is noteworthy that the separation by Pick of antibodies of various kinds and origins in the different globulin fractions has entirely failed of corroboration by Gibson.[9]

The fallacy of making positive conclusions in any work of this kind is shown by Gibson's statement that absolutely constant results can not always be obtained on successive repetition of the work.[10] This inability to secure checking results is a common experience in nearly all phases of immunity work, and yet with how much ease have many writers disregarded these failures and drawn conclusions without seeking for sufficient controls!

We may frankly admit, therefore, that we know nothing more definite concerning the nature of the antitoxin than we do of the nature of the toxin, except that we have very good reason to believe that its molecule is larger than that of the toxin, and there is much less opposition against holding that it is a protein. Antitoxins diffuse and dialyze much more slowly than do toxins; they seem to be destroyed by proteolytic enzymes, to behave in general like colloids, and in nearly all their properties they seem to be closely related to the serum globulins with which they are found associated. v. Behring[11] has also brought forward an interesting bit of evidence in favor of the protein nature of antitoxin, to the effect that antibodies do dialyze a very little, and that the diffusate may contain antitoxin, although it seems to be free from proteins, according to the usual chemical reactions. Ultramicroscopic studies, however, showed that proteins were present in such solutions, and that they varied in amount in direct proportion to the antitoxic action of the solution. This observation must be considered in connection with what has been previously stated concerning the failure to detect proteins by chemical reactions in solutions containing active ricin, because the delicacy of the chemical reactions is far below that of the biologic reactions.

Another point that bears on this subject, if we accept Ehrlich's theory that the antitoxins are identical with the receptors of the cells, is the observation that the tetanophile receptors of nervous tissue seem

9. Jour. Biol. Chem., 1907, iii, 233.
10. Proc. Soc. Exper. Med. and Biol., 1907, iv, 16.
11. Beitr. z. exper. Therap., 1905, x, 22.

to be destroyed by autolysis, at least the power to bind tetanus toxin is lost during this process.[12] Wolff-Eisner and Rosenbaum[13] found, however, that antitoxic serum itself is not affected by autolysis, which they ascribe to a difference between free and attached receptors, but which might, with equal propriety, be urged against the usual view that these substances are one and the same. However, the technical difficulties in these experiments present so many sources of error that one can not lay great weight on isolated observations.

As to the nature of the reaction between toxin and antitoxin, one would, indeed, be foolhardy who would attempt to decide even for himself the question that is now being disputed so vigorously, if not bitterly, between the schools of Ehrlich, Bordet and Arrhenius; but it is at least interesting to observe how many facts that are brought forward can be interpreted with equal facility in favor of either the absorption or the chemical union hypothesis. It would seem that the fundamental difficulty lies in the fact that the line has not yet been drawn between absorption phenomena and chemical reaction, even by the physical chemists working with simple substances of known composition; therefore, how premature it is to attempt to decide the very same question with mixtures of absolutely unknown nature and of extreme complexity!

The application of physical chemistry to this question by Arrhenius has shown at least one thing which has been seriously neglected in many studies, namely, the failure of toxin and antitoxin to unite completely with one another in the usual toxin-antitoxin mixtures. Field and Teague's interesting and important observations[14] on the migration of both toxins and antitoxins, and, for that matter, of practically all the other participants of immune reactions,[15] toward the cathode, does not point against the view that chemical reaction occurs between toxin and antitoxin, as these observations suggest. By no means all chemical reactions are between ions of opposite electric charges; indeed, in organic chemistry, and especially in biologic chemistry, the reactions generally concern non-ionic molecules.[16] We must appreciate that dissociation does not always mean ionization, and in organic chemistry the

12. Marie and Tiffenau (Compt. Rend. Soc. Biol., 1907, lxii, 1187) found that papain sets tetanus toxin free from brain tissue to which it has been bound.

13. Berl. klin. Wchnschr., 1906, xliii, 945.

14. Jour. Exper. Med., 1907, ix, 86 and 222.

15. Teague and Buxton: Jour. Exper. Med., 1907, ix, 254.

16. Bechhold (Münch. med. Wchnschr., 1907, liv, 1921) who confirms the results of Field and Teague, has also called attention to examples of interaction of inorganic substances of similar charges.

dissociation of inert molecules into chemically active molecules is a frequent observation.

This peculiarity of organic compounds is probably to be explained by the assumption now receiving favor among organic chemists, that the valences of the carbon atom are not all alike, but that they occur in pairs of opposite nature, thus $+\!-\!\overset{|}{\underset{|}{C}}\!-\!+$; consequently, an organic molecule can and does dissociate in such a way as to leave free two bonds, one of which is positively charged and the other negatively charged. As, for example, in the dissociation of ethyl alcohol, which is believed to take place as follows: $CH_3CH_2OH \rightarrow CH_3C\overset{+}{\underset{-}{H}} + H_2O$. Such a dissociated molecule is electrically neutral because of the opposite charges of the free valences, and, therefore, does not conduct electricity, and is not an ion, but it is tremendously active chemically. It is believed by Nef, and he has brought out an enormous amount of evidence to support his views, that it is this sort of dissociation that occurs in by far the greater number of interactions between organic substances, as well as in the action of enzymes. It would seem to be perfectly possible that large colloidal molecules, such as the proteins, may possess groups that ionize and impart electrical charges to the molecule as a whole, while, at the same time, reaction may occur between similarly charged molecules on account of the presence of such chemically active dissociated molecules, as Nef has described.

One can not refer to the application of physical chemistry to immunology without considering the recently published book of Arrhenius, which contains nearly all that has been done on this side of immunochemistry. The services of Arrhenius to physical chemistry have been so great, and the value of his work in this field is so unquestionable, that his views on the subject of immuno-chemistry must receive most careful consideration. Nevertheless, after reviewing this and other publications on the same topic, one can not fail to arrive at the conclusion that there is an irreconcilable difference between the exact methods of physical chemistry and the uncertain materials of immunology. Certainly one must admit that there have been numerous and serious errors in the work mentioned, and that there is a sound basis for Manwaring's[17] claim that we can not at this time apply the methods of physical chemistry to the study of serum pathology.

A number of the specific errors of Arrhenius's work have been

17. Jour. Biol. Chem., 1906, i, 213; Jour. Infect. Diseases, 1907, iv, 219.

pointed out by Michaelis,[18] among them being the following: First, in immunology we are probably dealing with colloids, of the type known as hydrophile in contradistinction to those that are more of the nature of suspensions. In solutions of colloids of this type the finest subdivisions do not consist of single molecules, or very small and constant groups of molecules, as is the case with simple solutions, but rather they are collected into aggregates of most uncertain and irregular size. This concept of the colloid solutions is disregarded by Arrhenius, who treats them as if they were true solutions. Therefore, when he speaks of two molcules of bound agglutinin being formed from three molecules of the free agglutinin, as is indicated by the equation derived from his experimental figures, he is probably not dealing with any such change at all, but rather with different sized aggregations of colloidal particles. It may be noted in this connection that Gibson obtained results in certain of his work with fractionation of antitoxins that suggested a variation in "the size or condition of aggregation of the colloidal globulin particles."[19]

Another case in error is shown by Michaelis, in that Arrhenius develops an equation for the precipitin reaction which indicates that it is similar to the precipitation of calcium from the solution of hydrate by CO_2, in which an excess of the precipitant redissolves the precipitate. In order to do this he must assume that the precipitin and the precipitate unite in definite quantities, one equivalent of precipitable substance uniting with one equivalent of precipitin to form one unit of the precipitate. This assumption is founded on the idea that the precipitate is of constant composition, which is altogether in contradiction to the facts. It is well known, and can positively be demonstrated, that the proportion of precipitin and precipitable substance in the precipitate vary within the widest ranges, and by no means according to the law of multiple proportions.[20] Furthermore, the precipitin and precipitable substance probably do not ordinarily unite with each other in anything like equivalent amounts, for it is well known that the precipitate is formed almost entirely from the constituents of the solution containing the precipitin, so that the term "precipitable substance," as ordinarily used, is altogether misleading.[21]

And, again, even if it were not common to the experience of every immunologist that many reactions fail to give duplicate results when

18. Folia Hematologica, 1907, iv, 225; Die Bindungsgesetze von Toxin und Antitoxin, Berlin, Gebr. Borntträger, 1905.
19. Banzhaf and Gibson: Jour. Biol. Chem., 1907, iii, 263.
20. Fleischmann and Michaelis: Biochem. Ztschr., 1907, iii, 425.
21. Moll: Ztschr. exp. Path. u. Therap., 1906, iii, 325.

repeated under nearly as possible the same conditions, we must admit the impossibility of any accurate quantitative measurements of the substances used in the immune reactions, or of the products of the reaction; but to prove the applicability of a law in physical chemistry corroboration by most exact analyses is necessary, and this is obviously impossible by the methods of serum pathology, which, at best, give but approximate results. Also, according to Manwaring,[22] the mistake has been made in applying the law of mass action to the phenomena of neutralization of toxin by antitoxin, and of lysins by antilysins, of neglecting to allow for the presence of free products of dissociation of the hypothetic compounds. The explanation of the so-called "Danysz phenomenon" in toxin-antitoxin neutralization, which has been adopted by Arrhenius and Madsen, who attempt to consider it on the basis of chemical reactions, is criticized by Craw,[23] who points out certain striking similarities to certain well-known absorption phenomena. For example, several pieces of paper added to a given amount of dye solution will take up more of the dye than will an equal amount of paper added at one time.[24] And, finally, and perhaps the most important of all, the physico-chemical explanations fail utterly when we come to consider the exquisite *specificity* of many of the reactions of immunology. It is interesting to notice the abrupt way in which Arrhenius dismisses this all-important feature, practically without consideration.

Even with the precipitin and agglutination reactions, which undoubtedly give the closest analogies to the processes of physical chemistry, the question of specificity stands up as a sphinx-like obstacle that has so far not been passed. Interesting observations have been made by Ivesco[25] on the precipitation of colloids of one electrical charge by colloids of the opposite charge, and Field and Teague[26] found that, while bacteria go toward the anode in the electrical stream, the agglutinins go toward the cathode, indicating that this reaction may be similar to the precipitation of oppositely charged colloids. But how is the specificity to be explained? Positively charged typhoid agglutinins agglutinate and precipitate negatively charged typhoid bacilli, but do not agglutinate cholera vibrios or colon and dysentery bacilli which are likewise negatively charged!

Nevertheless, the process of agglutination shows extensive resemblances to many physico-chemical reactions, especially brought out by

22. Jour. Infect. Dis., 1907, iii, 638.
23. Jour. of Hygiene, 1907, vii, 501.
24. Bayliss: Biochem. Jour., 1906, i, 221.
25. Compt. Rend. Soc. Biol., 1906, lxi, several articles.
26. Jour. exper. Med., 1907, ix, 222.

Bordet's early work, which showed that agglutination of bacteria by specific sera would not occur unless electrolytes were present. In other words, after bacteria have once been sensitized by agglutinin, they obey the same physical laws as the inorganic colloidal suspensions, which are characterized by being precipitated by the addition of traces of electrolytes. Possibly agglutinin makes the bacteria permeable for the electrolytes. According to Bechhold,[27] bacteria that have been sensitized by agglutinin are agglutinated half way between the poles of an electric current, this agreeing with the observations of Field and Teague that the bacteria and the agglutinin have opposite charges, which implies that the agglutinin-bacteria compound may be electrically neutral or amphoteric. As Neisser and Friedmann[28] say, bacteria and agglutinin behave like colloidal suspensions of opposite charges which form electrically amphoteric colloidal suspensions that are precipitated by ions of electrolytes, which discharge them unequally and cause flocking and precipitation. In their properties, especially in their relation to digestive enzymes, the agglutinins seem to be closely related to the serum globulins, with which they are always found in fractional precipitation of blood proteins.

The precipitins have aroused particular interest from the standpoint of chemistry, for they afford such a wonderfully delicate method of differentiating proteins that seem by all other methods to be identical; and this specificity has emphasized, as nothing else could, the absolutely individual nature of the proteins of the most closely related species and races, and even of members of the same species. On what part of the protein molecule this specificity depends is of the greatest biologic interest, especially now that Kossel and Fischer have given us an insight into the structure of this molecule, and a start on this problem has been made by Obermayer and Pick.[29] Their results suggest that the aromatic groups of the molecule are most closely related to the species specificity.

When the aromatic radicals of a protein are combined with various substances the protein loses the power to produce precipitins of such closely limited specificity for the original species, while retaining the property of producing precipitins with a wider range of action, in that they precipitate proteins coming from more than one species. This indicates that the striking specificity of proteins of different species depends on the aromatic groups of the protein molecule, and Vaughan has found

27. Ztschr. physikal. Chem., 1904, xlviii, 385.
28. Münch. med. Wchnschr., 1904, li, 465 and 827.
29. Wien. klin. Wchnschr., 1906, xix, 327.

evidence that the toxicity of the proteins depends on these same groups. Fleischmann[30] also found that tryptic digestion destroys this characteristic species specificity. It is interesting to consider that although the precipitin reaction itself so closely resembles the precipitation of one colloid by another of opposite charge, precipitins can not be produced for colloids other than proteins.

It is in the study of hemolysis, however, that the greatest amount of chemical investigation has been done, for many reasons. In the first place the simple chemical hemolytic agents had been known for a long time when the immune hemolysins were first detected, and naturally every attempt was made to bring the unknown agents into comparison with the known. Again, the similarity of hemolysis to the all-important processes of bacteriolysis made the more easily studied hemolytic processes the object of intense interest and activity.

The results of the studies of hemolysis have, from the chemical standpoint, led particularly to the development of an understanding of the importance of fats and lipoids in the immune processes. This development really originated in the observations of Hans Meyer and of Overton, which had disclosed the important influence exerted by the cell lipoids on the entrance of anesthetics into the cells, and the resulting physiologic action of the anesthetics. Shortly after Ransom (1901) found that the normal power of serum to decrease or inhibit the hemolytic power of saponin depended on the cholesterin that the serum contains, and thus introduced for the first time a definite substance as, in a sense, an antibody. Since then it has been found that cholesterin possesses more or less inhibiting power against a great variety of hemolytic agents, including not only the glucosides, but also simple chemicals, such as bichlorid of mercury, the hemolytic constituent of certain bacterial products, including especially tetanolysin, and of various organ extracts.

Kyes brought the action of complement into the same province when he demonstrated that lecithin acted as a most active complementing substance for the hemolytic constituent of cobra venom, and found a method of isolating an active amboceptor-complement compound in at least approximate chemical purity. His further studies[31] of this compound have demonstrated that the union of amboceptor and complement is chemical, at least in this case, for during the reaction between cobra venom and lecithin free fatty acids are split out of the lecithin molecule; in the completely saturated lecithid, however, the amount of venom constituent is so minute in proportion to the amount of lecithin radicals,

30. Ztschr. klin. Med., 1906, lix, 515.
31. Biochem. Ztschr., 1907, iv, 99.

with which it is combined, that the figures for the elementary analysis of the compound do not differ appreciably from those of monostearyl lecithin itself. Other compounds are also formed in which the proportion of lecithin is not so great, and analysis of these "incomplete lecithids" may possibly throw some light on the nature of the venom component.

It is interesting to note that the presence of even a small amount of lecithin, combined with the hemolytic amboceptor, renders the latter incapable of combining with antivenin. The molecular weight of the complete lecithid is between 2,000 and 3,000, and as lecithin has a molecular weight of only about 500, it would seem that several molecules are united in this compound. Teruuchi[32] has made the interesting observation that an active mixture of pancreatic juice and succus entericus, which digests both proteins and lecithin, will not attack the cobra lecithid compound. Morgenroth and Carpi[33] also found that pepsin does not destroy the cobra lecithid, although it does attack the hemolytic constituent of untreated venom.

Recently the observations concerning the relations of lipoids to hemolysis have been frequent and numerous. von Eisler[34] found evidence that the inhibiting cholesterin of the serum is probably for the most part bound to the proteins, and that cholesterin esters do not have this property of inhibition. Neuberg[35, 36] has found that lipolytic substances have very considerable hemolytic powers, and, conversely, that the bacterial, animal, and vegetable hemolysins are lipolytic, or at least that the fluids in which they are contained also contain lipolytic substances. Pascucci[37] demonstrated by studies of artificial lipoid membranes that the hemolytic influence of the saponins depends on the lipoids in the membranes of the red corpuscles. Morgenroth and Reicher[38] have shown that cholesterin given by mouth will decrease the amount of anemia produced by cobra-lecithin and suggest the use of cholesterin as a therapeutic agent against toxic anemias.

Woelfel[39] found alcohol-soluble hemolytic substances in blood serum, and other investigators have found that alcoholic extracts of various or-

32. Ztschr. physiol. Chem., 1907, li, 478.
33. Biochem. Ztschr., 1907, iv, 248.
34. Ztschr. f. exp. Path. u. Ther., 1906, iii, 296.
35. Neuberg and Rosenberg: Berl. klin. Wchnschr., 1907, xliv, 54.
36. Neuberg and Reicher: Biochem. Ztschr., 1907, iv, 281; Münch. med. Wchnschr., 1907, liv, 1725.
37. Hofmeister's Beitr., 1905, vi, 543 and 552.
38. Berl. klin. Wchnschr., 1907, xliv, 1200.
39. Jour. Infect. Dis., 1905, ii, 97.

gans and tissues are hemolytic. Friedmann[40] and Wohlgemuth[41] have found that pancreatic juice contains a hemolysin that has properties similar to an ordinary hemolytic amboceptor, in that it may be activated by lecithin, and a similar hemolysin is also present in the pancreas itself (Noguchi[42]). In many of these cases, as with the action of lipase and fatty acids described by Noguchi, the hemolytic action probably depends on the formation of free fatty acids, which are themselves strongly hemolytic. Finally Noguchi[43, 44] has found that the soaps extracted from serum and tissues, when mixed with serum itself, have properties that in many respects resemble the complements. Indeed, he finds many resemblances to complements in all substances of this class, so that he suggests the possibility that at least certain serum and cellular complements may actually be salts of the higher fatty acids with weak organic bases. This suggestion may be related to the observation of Hektoen[45] that complement may be inactivated by the action of barium, calcium, strontium and magnesium ions, which are all precipitants of fatty acids.

The inhibitive action of normal serum on immunity reactions and allied processes is by no means limited to the inhibition of saponin hemolysis by cholesterin. Enzyme reactions are notoriously inhibited by normal serum, and the presence of large quantities of serum is of similar influence in other processes. These effects are not all due to cholesterin, and it is generally assumed that the proteins are the chief inhibitive agent, while the presence of anti-enzymes, anti-complements, anti-immune bodies, etc., in normal serum, seems to be generally accepted, these various anti-substances being supposed to be in some cases specific and in more cases not specific.

There is one highly important property of normal serum, and as it does not seem to have been taken into consideration as yet by any of the writers on immunology, I may refer to it at this time. This is the remarkable property of the blood serum to *suppress ionization*. It has been well established by physical and chemical measurements that the blood is not alkaline under ordinary circumstances, and it probably never is either actually appreciably alkaline or acid under any conditions whatever during life, for the occurrence of anything but a neutral reaction would certainly terminate life at once. Acidity and alkalinity are not

40. Deutsche med. Wchnschr., 1907, xxx, 585.
41. Biochem. Ztschr., 1907, iv, 271.
42. Biochem. Ztschr., 1907, vi, 185.
43. Jour. Exp. Med., 1907, ix, 436.
44. Biochem. Ztschr., 1907, vi, 327.
45. Trans. Chicago Path. Soc., 1903, v, 303.

matters of color reactions with indicators, as has been too commonly assumed, but these terms indicate the presence of an excess of either hydroxyl or hydrogen ions in a solution, which ions affect our indicators variously, according to the chemical nature of the indicator used. It is impossible, at this time, to go into the proofs of these statements, and I can only explain to the extent of saying that the composition of the blood is, with apparent purposefulness, so ordered that neither free hydrogen ions nor free hydroxyl ions can exist in the blood in excess of the other to any appreciable amount; the blood is really almost quite as neutral as pure water, in which the few hydrogen and hydroxyl ions balance one another. Henderson and Black[46] estimate that the amount of either hydrogen or hydroxyl ions free in excess in the protoplasm is not over five parts in 10,000,000,000.

This condition of neutrality is maintained, in spite of the diversified chemical processes of the body which constantly tend to produce either acidity or alkalinity, through the action of at least three sets of serum constituents, namely, the carbonates, the phosphates and the proteins. The carbonates and the phosphates owe their property of suppressing ionization to the readiness with which they take up free ions of either hydrogen or alkali metals, and pass into compounds that have a greater or less number of hydrogen ions, but that do not dissociate readily to liberate these ions, namely, the mono, di and tribasic phosphates and the mono and dicarbonates. The proteins play a similar rôle because of their ability to bind either positive or negative ions and to form compounds with them that dissociate but little.[47]

As far as the action of enzymes is concerned, we have good reason to believe that the presence of free ions is necessary, or is at least favorable, for speed of reaction. Note, for instance, the importance of free hydrogen ions for the action of pepsin and of the autolytic enzymes, and of hydroxyl ions for trypsin. Of course, in the reactions of immunity we do not know whether or not ionization is an essential accompaniment, but we have excellent comparative grounds for believing that it is, since even in the case of the interaction of non-ionic active organic molecules the necessary dissociation of the molecule seems to be favored by the action of free ions, especially hydrogen and hydroxyl ions. May not this power of suppressing ionization, that is possessed by serum, be of importance in the phenomena of inhibition exhibited by normal serum against the reactions of immunity? I have already found reasons for

46. Amer. Jour. Physiol., 1907, xviii, 250.

47. An excellent discussion of this topic is given by Moore et al., Biochem. Jour., 1906, i, 285-295.

believing that it is a factor to be reckoned with in the inhibitive action of normal serum on autolytic enzymes, and would suggest that it receive consideration by those who are studying other phenomena that occur in the presence of blood serum. I may mention that this inhibitive power of the blood is very limited in amount, for the small quantity of carbonates and phosphates is soon saturated, and so a large excess of serum is necessary to check any process by which either free hydrogen or hydroxyl ions are being liberated. For example, in the autolysis of exudates, as studied by Opie, the autolysis is held in check only in the presence of a very large excess of serum. If the amount of serum is small the inhibitive action is only temporary.

One can not conclude without at least referring to the recent developments along the line of immunization against non-protein compounds. Although earlier investigators sought for immune bodies in the serum to account for the increased resistance against arsenic, morphin and similar poisons, yet the results were all negative, except for a few incorrect claims of immune sera against morphin. So constant were all these failures that at last it came to be accepted as a settled fact that no immune body could be obtained, except for proteins, or at least very closely related substances in case toxins and enzymes were found to be non-protein. To be sure, Kobert found a slight increase in the inhibitive action of the serum of animals immunized to saponin, which was ascribed to an increase in the cholesterin of the blood, perhaps derived from the excessive hemolysis that the saponin had produced, but even this modest result has not been fully confirmed.

More recently certain French authors[48] have described the development in animals immunized to bile or bile salts, of a slight degree of protective power in the serum, but Bermbach[49] controverts this claim. Champy[50] also claims to have obtained by repeated injections of the potassium salt of cantharadin, in 3-7 mg. doses into rabbits, a serum which in 20 c.c. doses protects against 1 mg. of the cantharadin, but not against 2 mg. One would hardly speak of this as immunizing! Ford,[51] however, has found that 1 c.c. of serum from a guinea-pig immunized against an aqueous extract of *Amanita phalloides* neutralizes from five to eight times the lethal dose of this extract, the active principle of which is a glucoside. He has also secured an antitoxic serum against the active principle of *Rhus toxicodendron*, which is also a glucoside, with about

48. Nicolle: Ann. Inst. Pasteur, 1907, xxi, 26.
49. Pflüger's Archiv., 1907, cxviii, 205.
50. Jour. d. Phys. et Path. gen., 1907, ix, 807.
51. Jour. Infect. Dis., 1907, iv, 541.

the same degree of efficiency as shown by the serum against *Amanita*. Further studies from this source will be awaited with great interest, especially since so many unsuccessful attempts have previously been made to secure antisera for the hemolytic glucosides of the saponin group. It will be noticed that the degree of activity of these immune serums does not compare with that obtained against the true toxins of more complex nature.

In this connection may be mentioned the very striking and fundamental difference that exists between the defense of the body against the poisons of the toxin class and those of simpler chemical structure. Besides the quantitative difference in favor of the immunity against the complex toxins, and the failure of acquirement by the serum of the power of neutralizing or binding the simple poisons, we note also the entire lack of purposeful development of special substances to meet a special condition. Nearly all the simple poisons are inhibited or rendered inactive, to a greater or less extent, in one way or another, after they enter the body, but the substances that accomplish this do it in a casual way. These substances which bind or neutralize the poisons are, for the most part, themselves simple constituents of the body or products of its normal metabolism, e. g., sulphates, glycocoll, bile acids, glycuronic acid, ammonium salts, etc., which happen to have binding power for one or more of the poisons. If these poisons enter the body they combine with the neutralizing substance as far as the amount of this suffices, which is generally very incompletely. There does not follow, however, any evident increase in the amount of this protective substance, and the excess of poison acts unhindered. There is no such special adaptation to meet a pathologic condition as occurs in infections, and hence there is no resistance against simple poisons, even in the most extreme cases of drug habituation, that compares with the resistance to such diseases as smallpox, scarlet fever, etc.

NO MARCH NUMBER.

This number of the Archives of Internal Medicine—which should be the March number—has been unavoidably delayed. The Postoffice rulings require that it bear the date of the month of issue, which will explain why this appears as the April number. While there will be no March number, each volume will consist of six numbers as announced.

ROLE OF VENOUS CONGESTION IN COMPENSATION OF TRICUSPID INSUFFICIENCY.

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The possibility of the establishment of compensation in the lesions of the tricuspid valve was doubted by Romberg (Cf. Franke[2]) and hesitatingly admitted by Krehl (Cf. Franke[2]) on account of the weakness of the right auricle, which is the only cavity of the heart left to perform the task. MacKenzie[1] and others have, however, described cases of tricuspid insufficiency lasting over long periods. Recently, Franke[2] has cited several cases where, in the light of the literature, he believes that dilatation and hypertrophy of the right auricle and ventricle, venous congestion, and especially congestion of the liver were factors in maintaining compensation.

The clearness with which the rôle of venous congestion as an element in compensation is demonstrated makes the following case worthy of record:

History.—The patient, an adult white female with a long-standing heart lesion, developed ascites. There was mitral insufficiency, secondary tricuspid insufficiency, and enlargement of the heart which extended beyond the anterior axillary line. The usual murmurs were present. The jugulars were greatly distended. Shortness of breath had been pronounced for many months. Edema of the lower extremities, varying in extent, had been present for a long time. There had been periods of broken compensation.

With the onset of swelling of the abdomen, these signs were not materially changed. The patient had not been seen for a number of weeks when, on account of urgent dyspnea and rapid action of the heart, the physician was called.

Examination.—The heart was slightly displaced upward. The action was so tumultuous that, on auscultation, nothing could be determined with certainty. No radial pulse could be found. The jugulars were collapsed in diastole, and in systole presented a very large wave. The face was pale and the lips showed but a little color. There were no signs of congestion about the face, neck or upper extremities. Dyspnea was distressing. The abdomen was greatly distended and tense, the subcutaneous edema extensive. The lower extremities were greatly swollen and shapeless.

Treatment.—The abdomen was tapped and immediately after the pressure was reduced the following conditions were noted: The rate of the heart's action became regular and slower; the radial pulse returned. On auscultation, half an hour later, the murmurs had returned. The jugulars were greatly distended and the systolic pulsation reduced in extent. The face was at first congested, with the

1. Am. Jour. Med. Sc., 1907, cxxxiv, 12.
2. Wien. klin. Wchnschr., 1906, xix, 956.

lips blue. Within a few minutes, however, the lips became red and the respirations were slower, deeper and easier. After the first reaction the patient became more comfortable.

The points of especial interest in this case appear to be the following:

1. (a) The congestion of the superior cava, caused by the cardiac lesion, continued until the abdominal pressure obstructed the inferior cava, after which the branches of the superior cava were freely drained by the heart. (b) The congestion of the superior cava reappeared as the obstruction of the inferior cava was removed by reducing the abdominal pressure. (c) The diminution of the congestion of the superior cava was followed by a large systolic venous pulsation which diminished in extent as the congestion returned.

2. The heart's action was phenomenally tumultuous and the quantity of blood delivered to the arteries was very small; there was no palpable radial pulse.

3. Withdrawal of fluid from the abdomen was followed by congestion of the veins and lips, a retardation of the heart's action, a very great improvement in the character of the radial pulse, and a relief of the dyspnea.

4. The previous history pointed to the existence of tricuspid insufficiency.

Physiologic data show that the capillary pressure may vary from zero to 50 mm. of mercury, ranging under normal conditions from 10 to 30 mm. If a ligature be placed about a finger, the capillary equals the static arterial pressure. It is, moreover, fallacious to argue that a fall of arterial pressure necessarily produces a fall of pressure in all of the capillary areas of the body.[3] The capillary pressure is normally from one-sixth to one-third of the arterial pressure.

The venous pressure is also influenced by the arterial pressure. Schäfer[4] says: "When all the venous exits from any part are ligated, then the pressure rises, peripherally to the seat of ligation, to the arterial pressure."

If the pressure in an obstructed vein from any part may rise to the arterial pressure, the same principle should apply to the entire venous system. This has been shown to be true by Cohnheim's[5] experiments on pericardial pressures. Cohnheim inserted canulæ in the pericardium, femoral artery and jugular vein. Oil was injected into the pericardium and pressures were measured in millimeters of oil for the pericardium,

3. Schäfer, Text-Book of Physiology, ii, 116.
4. Vol. i, p. 121.
5. Allgemeine Pathologie, 1882, Bd. I, 22.

in millimeters of mercury for the femoral artery, and in millimeters of soda solution for the jugular vein. The results were as follows:

1. Thirty mm. of oil pressure was taken up by the elasticity of the pericardium without change of pressure in either the femoral artery or jugular vein.

2. Sixty to 70 mm. of oil pressure caused a drop of 20 to 30 mm. of mercury in the femoral artery and a rise of 60 mm. of soda solution in the jugular vein.

3. One hundred to 120 mm. of oil pressure produced a fall in the femoral pressure to half its original height and a rise to 100 mm. of soda solution in the jugular vein.

4. Two hundred and forty to 320 mm. of oil pressure caused a cessation of pulsation in the pulmonary artery, but the femoral continued to pulsate and registered a pressure of from 10 to 15 mm. of mercury; the venous pressure was 220 to 240 mm. of soda solution.

On removing the pericardial pressure the circulation returned to its original condition, save for a few minutes when the arterial pressure was above its original point. If in (4) the femoral pressure is converted into terms of soda solution, 133 to 200 mm., it is apparent that the venous pressure equals the arterial when the flow from the veins is blocked and the system becomes a closed pipe. In other words, the circulation in the systemic arteries, capillaries and veins is really one and is controlled by the same principles as those governing the action of fluids in an open or closed system of pipes.

In a closed system the pressure is the same throughout, as illustrated in Cohnheim's experiment when the venæ cavæ were blocked, as in (4). Here the pressure in the cavæ and arteries was equal. In a partially closed system the pressure in the end distal to the pressure head is equal to that of the pressure head minus friction and flow. In Cohnheim's experiment the venæ cavæ were partially closed as in (3). The decreased flow of blood caused the arterial pressure to fall and the venous pressure to rise. The system being partially closed, the pressure throughout was proportionately equalized. In the normal condition the open ends of the system, the venæ cavæ, register zero or less. Here all of the pressure head is consumed in friction and flow.

The storage of blood in the veins is due to the arterial flow, and the pressure under which the blood is maintained in the veins is the arterial pressure minus friction and flow. The venous congestion may be compared to a closed system in which, while the blood is stationary, the pressure represents potential energy; while flowing, kinetic energy. During life, venous congestion is associated with and to a degree equal to the

active force obstructing the flow of blood in the vein. It represents the potential energy of the arterial pressure or left ventricle, transferred from source of power of a partially closed tubular system to the distal end, to be used, as kinetic energy, in overcoming or compensating the force obstructing the flow of blood in the vein. The left ventricle compensates venous obstruction.

Supported as it is, this theory as to the nature of venous congestion should form a safe basis for a consideration of some of the mechanics of pathologic circulatory changes. It is generally acknowledged that mitral insufficiency is usually associated with hypertrophy and dilatation of the left auricle and ventricle, pulmonary congestion and varying degrees of hypertrophy of the right ventricle (compare Mority[6]). In tricuspid insufficiency, hypertrophy and dilatation of the right auricle and ventricle may be compared with the similar changes in the left heart in mitral insufficiency; while the general venous congestion may be regarded as analogous to the pulmonic congestion. The rôle of the right ventricle in mitral lesions has, however, no counterpart in disease of the tricuspid valve. Both Stadler[7] and Franke[2] assert that, because of atrophy, it is impossible for the left ventricle to play a part in the compensation of tricuspid insufficiency.

In the case cited, the course of events was probably somewhat as follows: There was hypertrophy and dilatation of the heart, tricuspid insufficiency and intense venous congestion. The development of a terminal ascites gradually obstructed the inferior cava. As this obstruction developed, the flow of blood to the heart diminished until the superior cava and its branches were relieved of their former congestion, thereby removing all traces of congestion from the head and upper extremities. The jugular vein was collapsed in diastole, and in systole a large pulsation, due to backflow from the right ventricle, was present. The presence of the backflow into the superior cava which was not congested shows that, when the tricuspid lesion had developed, the backflow takes no part in the causation of congestion.

In this case the superior cava was an open system in which the pressure at the extremity distal to the power should be low; while the power was much reduced, thereby diminishing the amount of blood which could, under low pressure, be forced through the capillaries. The low arterial pressure was indicated by the absence of radial pulse. The right ventricle was competent to move forward all the blood delivered by the venæ cavæ, as was shown by the condition of the superior cava. This

6. Deutsch. Arch. f. klin. Med., 1899, lxvi, 421.
7. Deutsch. Arch. f. klin. Med., 1905, lxxxiii, 71.

competency of the right ventricle was due to rapid and forcible action of the heart. The low pressure in the superior cava developed when the amount of blood delivered to the systemic veins was less than that delivered to the pulmonic artery. The inferior cava, obstructed by the peritoneal pressure, was congested by a pressure which, undoubtedly, was equal to the low arterial pressure; and the circulation in the lower portion of the body was almost *nil,* as indicated by the extreme edema.

The absence of congestion of the superior cava, its presence in the inferior cava as a result of ascites, and the existence of the backflow which had no appreciable effect on the circulation in the superior cava, suggest that, in tricuspid insufficiency, the activity of the right ventricle may be considered under two heads: 1. The effort expended in pumping blood into the pulmonic artery. This factor is deficient as compared with the normal and is the immediate cause of venous congestion. 2. The effort expended in propelling the regurgitant blood into the auricle and veins. The production of this backflow acts mechanically by increasing, first, the auricular and, later, the auricular and venous pressure so as to build, at the tricuspid opening, a wall, so to speak, of blood under high pressure, which, in part, takes the place of the tricuspid valve. This may be regarded as a utilization of a portion of the congested blood.

The large systolic venous pulsations, the absence of radial pulse and the forcible rapid heart action show that only a small amount of blood was delivered to the arterial system and that a large portion of the blood was returned during each systole to the veins and right auricle in which the pressure was low. Hypertrophy and dilatation of the right ventricle and, as MacKenzie[1] suggests, the right auricle, were the only active compensatory factors. They were unequal to the task, leaving the heart to exhaust itself by rapid action which moved a minimum amount of blood and delivered a minimum amount of nutrition to the heart.

When the abdominal pressure was relieved, congestion in the venæ cavæ and distention of the right auricle were immediately re-established, thus furnishing a pressure of a degree sufficient to diminish the tricuspid regurgitation and to raise the pressure in the right ventricle to such an extent that a larger amount of blood was delivered to the pulmonic circulation and left heart. The dyspnea was then diminished; the heart's action was reduced in rate and regular, the radial pulse returned, and the large systolic venous pulsation was diminished in size.

It should be noted that, after the abdominal pressure was removed, the right ventricle had sufficient strength to perform the required work; it must consequently be inferred that the ventricle had the power necessary to pump the usual amount of blood while the inferior cava was ob-

structed. But during this period the low pressure in the auricle and superior cava offered the path of least resistance for the greater portion of the small amount of blood delivered by the superior cava. Venous congestion is the resistance on which the hypertrophied right ventricle must depend for support.

The right ventricle would thus appear to depend on venous congestion of a degree sufficient to maintain a pressure which, with the addition of that contributed by the backflow, may offer resistance enough to act as a substitute for the insufficient tricuspid valve. Now, since the venous congestion depends on, is caused by and represents the arterial pressure, minus friction and flow, or, in other words, the activity of the left ventricle, it follows that in tricuspid insufficiency the left ventricle bears the brunt of that part of compensation which is played by venous congestion.

As the flow of blood to the left heart is diminished, the work of the left ventricle is progressively lessened. The left ventricle may, therefore, remain of normal thickness or it may become atrophied. The large normal excess of arterial pressure over that in the capillaries renders it possible that even with diminished activity of the left ventricle and a lowered arterial pressure there may yet be a rise in venous pressure, a portion of which is utilized for compensation, the balance being consumed through friction and flow of blood.

The factors in tricuspid compensation usually considered[8] are: 1. Hypertrophy and dilatation of the right auricle. 2. Venous congestion. 3. Hypertrophy and dilatation of the right ventricle. 4. Aspirating effect of the thorax with inspiration.

1. As the tricuspid valve begins to leak, the right auricle is distended and hypertrophies to some extent. But when the lesion becomes extensive, as in this case, the auricle plays a minor rôle, if, indeed, it plays an active part at all; it is, however, probably inactive, as shown in one case by Franke,[2] and especially noted by MacKenzie.[1] If inactive, it virtually becomes a portion of the venous system.

2. The venous congestion, compensatory venous congestion, may be considered under two heads: (a) the constant or accumulated (diastolic) pressure from the arterial system, and (b) the pressure added by the backflow from the right ventricle.

These pressures serve two purposes: First, the constant pressure maintains the venous distention, so that, with the backflow of blood under a relatively high pressure, the venous pressure rapidly rises to a

8. Sahli: Diagnostic Methods. Transl. by Kinnicutt and Potter from fourth German edition, 1905, 335.

maximum, after which the greatest possible amount of blood enters the pulmonary artery. Second, the maximum venous pressure aids in filling the ventricle during diastole. Through its elasticity, experimentally shown by Salamon,[9] the liver in the pulsating venous system serves the same purpose as an air chamber in a force pump; it also supplies storage for blood.

3. Hypertrophy of the right ventricle is required to develop the added systolic venous pressure and to perform the extra amount of work due to the size of the ventricular cavity when there is dilatation. Here, to propel the usual amount of blood, the muscle or power moves over a shorter distance, consequently must do more work. A certain amount of dilatation is necessary for compensation, supplying space for the blood which is returned in systole to the auricle and veins. Dilatation beyond this point furnishes storage room for blood.

4. Aspiration with inspiration is a minor factor.

5. To this test should be added the work of the left ventricle which is represented by the venous congestion.

Of these factors, the venous congestion and the hypertrophy and dilatation of the right ventricle are the most important. Impairment of either factor leads to heart failure, each in its own way.

In the one event the heart, deprived of the venous pressure against which it works, exhausts itself by increased activity and an ever-diminishing amount of nutrition until it can no longer contract. At autopsy the heart and cavæ should contain little blood. In the other event, if the right ventricle fail, the right heart and veins are so distended with blood that the weakened heart muscle is unable to contract. At autopsy the right heart and veins are distended with blood, while the left heart contains little or no blood.

CONCLUSIONS.

In tricuspid insufficiency the left ventricle and venous congestion play the same rôle as do the right ventricle and the pulmonary congestion in mitral insufficiency. In the latter condition the congestion of the auricle and the pulmonary circulation furnishes the resistance against which the hypertrophied left ventricle works; in the former the congestion of the right auricle and cavæ favor the action of the hypertrophied right ventricle.

In the one, the right ventricle causes the pulmonic congestion; in the other, the left ventricle, the caval congestion. This is as it should be, for in each circulation the ventricle is best fitted to develop the neces-

9. Salamon: Lancet, London, 1907, I. 4.

sary venous pressure. The remaining factors have a temporary or minor influence on the compensation of insufficient mitral and tricuspid valves.

SUMMARY.

Mitral Insufficiency.

L. auricle. { Dilatation. / Hypertrophy.

L. ventricle. { Dilatation. / Hypertrophy.

Pulmonic veins, congestion.

Pulmonic artery, congestion.

R. ventricle, hypertrophy.

Increased resistance.

Tricuspid Insufficiency.

R. auricle. { Dilatation. / Hypertrophy.

R. ventricle. { Dilatation. / Hypertrophy.

Systemic veins, congestion.

Systemic arteries, low pressure.

L. ventricle, normal or atrophied.

The normal margin of arterial pressure above that in the capillaries makes possible a decrease in the arterial pressure (l. ventricle either normal or atrophied) in the presence of a rise in the capillary pressure, until the venous, capillary and arterial pressures are relatively the same, or until the flow of blood through the capillaries is insufficient to sustain life.

TUBERCULOUS ULCER OF THE STOMACH, WITH REPORT OF A CASE.*

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According to Boas, three forms of tuberculosis of the stomach may be distinguished: the tuberculous granulomata (the rarest form), miliary tuberculosis of the gastric mucous membrane (the most frequent form), and finally tuberculous ulcer of the stomach.

The comparative rarity of tuberculous ulcer of the stomach may be gathered from the following facts: Hamilton,[1] in a careful study of the reported cases, was able to collect but 15 positive and 9 doubtful. Blumer[2] collected but 30 reliable instances. Arloing,[3] in his classic thesis, gives 147, but he was not so discriminating as the writers mentioned above and included a number which they had rejected. In view of the generally accepted fact that tuberculosis of the stomach is practically always secondary to a tuberculous process elsewhere, the autopsy records on tuberculous patients is of value here:

Simmonds	8 cases in	2,000	autopsies.
Steiner and Neurcutter	4 cases in	302	autopsies.
Widerhofer	2 cases in	418	autopsies.
Soltau Fenwick	2 cases in	2,000	autopsies.
Papavoine	1 case in	50	autopsies.
Villegk	5 cases in	1,317	autopsies.
Barthez and Rilliet	6 cases in	141	autopsies.
Müller and Hecker	8 cases in	297	autopsies.
Gerhardt	2 cases in	418	autopsies.
Still	5 cases in	226	autopsies.
	43 cases in	7,169	autopsies = 0.7 %.

It would appear from Arloing's collected figures that tuberculosis of the stomach is more common in general miliary tuberculosis than in the chronic forms; thus Simmonds, among 100 cases of general miliary tuberculosis, found one instance where the stomach had been attacked. Frerichs noted 3 among 30 cases of miliary tuberculosis and only 7 in 250 of the chronic form.

* Read before the Medical Society of the District of Columbia, February, 1908.

1. Bull. Johns Hopkins Hosp., April, 1897, p. 75.
2. Albany Med. Ann., 1898, p. 145.
3. Thesis, Lyons, 1902-3.

As to whether tuberculous lesions of the stomach are more common in children or in adults, we may again borrow from Arloing. His collected figures show that in 2,115 autopsies on tuberculous children there were 38 instances of stomach involvement (1.7 per cent.), while in 4,917 autopsies on tuberculous adults there were but 23, or 0.45 per cent. In spite of these figures, this author is of the opinion that the condition is more often seen in adults.

As to the favorite location of the ulcers there is some difference of opinion. Ricard and Chevrier,[4] from their collection of statistics, found that the pyloric region extending one or two centimeters from the opening was involved in about 35 per cent. of the cases; then the greater curvature, 20 per cent.; then the posterior surface, the lesser curvature, the anterior surface, and the subcardiac region. Tripier would place the lesser curvature immediately after the pylorus in frequency of involvement. The apparent preference for the pyloric end of the stomach has been explained by Virchow and Rokitansky as due to the more numerous lymphatic follicles in this locality.

HISTORIC DATA.

The first mention of tuberculous ulcer of the stomach is said to have been made by Andral and Cruveilhier in their treatise on pathologic anatomy in 1842. Since that time brief reference has been made by various authors of text-books to this condition. Bignon in 1853 published the first detailed account of a case of tuberculous ulcer of the stomach. Litten and Talamon in 1879 reported cases in which giant cells were found in microscopic examination of sections from ulcers. Coats[5] in 1886 inaugurated a new era by demonstrating the specific bacilli in the lesions. Musser's[6] case, the report of which appeared in 1890, was the first published in America in which Koch's bacilli were found.

In looking up cases recorded as tuberculous ulcers of the stomach, one is confronted with the difficulty of determining their authenticity. At the risk of excluding some in which there is little doubt as to the genuineness, it would seem best to accept only those in which a microscopic examination shows either a typical tuberculous picture or the tubercle bacilli in the walls of the ulcer. This careful scrutiny seems the more necessary when we realize that the generally anemic and depraved physical condition of tuberculous patients renders them exceptionally good subjects for simple ulcer of the stomach. It is very likely

4. Rev. de chir., 1905, xxxi, pp. 74 and 557.
5. Glasgow Med. Jour., 1886, xxvi, p. 53.
6. Phila. Hosp. Rep., 1890, i, p. 117.

that not a few phthisical patients suffer from peptic ulcers and the finding of the bacilli on the surface of such ulcers is no proof of their being truly tuberculous, as shown by Blumer and Happel's[7] case of pulmonary tuberculosis associated with round ulcer of the stomach.

MODE OF INFECTION.

There are four avenues by which tuberculous infection might reach the stomach, viz.: by direct infection of the mucous membrane, through the lymphatics, through the blood stream, and through the serous coat.

The first-mentioned mode of infection might appeal to us strongly because of the apparent ease with which the bacillus might be brought in contact with the mucous membrane of the stomach by the swallowing of infected sputum by those whose lungs are tubercular, and in infected food, but the best authorities do not consider this the usual manner. Arloing,[3] in his experiments on dogs, was unable in a single instance to produce ulcer of the stomach by administration of infected materials, his experiments including mechanical irritation and devitalization of areas of the mucosa by ligation of vessels and alterations in the chemical reactions of the gastric juice.

Through the lymphatic system the bacilli might gain entrance directly into the lymphatics of the stomach, or through the contiguity of an infected lymphatic gland; thus a tuberculous gland may become adherent to the wall of the stomach and ulcerate through. In our case there were three large caseous glands behind the ulcer, one of which was closely adherent to the floor of the ulcer and showed microscopic communication with it.

Infection through the blood stream is believed by Arloing to be the most usual method. To support this theory, he brings the fact that in his numerous experiments on animals he was but twice able to produce a tuberculous gastric ulcer, and in both of these cases the bacilli had been injected into the blood stream. In one there had also been an intraparietal injection. One of these artificially produced ulcers was situated in the duodenum, but to all intents and purposes a duodenal ulcer is practically the same as a gastric ulcer. The fact that tuberculous gastric ulcers are more common in acute miliary tuberculosis also strengthens this theory. Infection through the serous coat of the stomach is admitted as at least possible, although certainly very unusual.

We wish here to report a case of large single tuberculous ulcer of the cardiac end of the stomach without pulmonary involvement.

7. Albany Med. Ann., 1898, p. 594.

Patient.—M. J., aged 18, female, single, was admitted to the Garfield Memorial Hospital April 12, 1907.

Family History.—Negative.

Previous History.—Diseases of childhood; otherwise healthy.

Present Illness.—The patient has not been well for the past few months, but is unable to state exactly when illness began. Appetite has been poor. Has lost weight greatly. Was treated in Freedman's Hospital for three weeks about three months ago (does not remember exact date), and at that time she had persistent vomiting which occurred a few minutes after taking food or water and was not accompanied by nausea. There was diarrhea. Vomitus and dejecta sometimes contained blood (?). Now she complains of pain in throat, particularly on swallowing. There is vomiting and diarrhea, but not so severe as formerly. There is no cough but she raises considerable mucus from throat. She complains of a swelling in the upper part of the abdomen. Owing to the patient's low grade of mentality and weakened physical condition, the history was obtained with difficulty and is unsatisfactory.

Physical Examination.—Emaciation extreme. Slight exophthalmos. Tongue clean, smooth and red. Pulse small, regular and frequent. Heart normal. Lungs normal. There is a distinct protrusion in the epigastric region, the most prominent point of which is in the median line, one-third of the distance from the xiphoid to the umbilicus. The abdominal wall is extremely tense, especially over the above-mentioned area. There is marked tenderness on pressure over the tumor, which is smooth and conforms in its general outline to an enlarged liver (which it later proved to be). The lower border of the right lobe of the liver is found to be on a level with the umbilicus; the lower border of the left lobe about two inches higher. Liver dulness begins above in the nipple line at the fifth interspace and extends downward to a horizontal line just above the umbilicus. The left lobe extends to a point about two inches higher. There is dulness over the lower portion of Traube's semilunar area. Posteriorly the liver dulness extends below its normal position. The spleen can not be distinctly outlined. There are no superficial glandular enlargements. Knee jerks are absent. The record of the pulse, respirations and temperature were of no value from a diagnostic point of view. There was vomiting and diarrhea with involuntary movements. The various examinations in the clinical laboratory threw but little light on the case. These were as follows:

SPUTUM: April 14.—Negative to tubercle bacilli.

VOMITUS: Very sour fluid with strong acid reaction. Contains milk curds and a large amount of mucous of a purulent character. Trace of lactic acid. Microscopic examination showed numerous leucocytes, no red cells, numerous large bacilli, sarcinæ and other organisms.

BLOOD: April 6.—

Hemoglobin	80 per cent.
Red cells	4,848,000
Leucocytes	15,200

April 15.—

Hemoglobin	70 per cent.
Red cells	4,920,000
Leucocytes	28,200

Differential leucocyte count, 500 cells:

Small lymphocytes	16.0
Large lymphocytes	2.8
Transitional	1.0
Polynuclear	80.0
Eosinophile	.2
	100.0

URINE: April 6.—Acid reaction. Specific gravity, 1015. Albumin, 7 per cent. Granular casts. Numerous leucocytes.

April 13.—Acid reaction. Specific gravity, 1007. Albumin, 5 per cent. Hyaline and granular casts. Numerous leucocytes.

April 17.—Acid reaction. Specific gravity, 1015. Albumin, 8 per cent. Granular casts. Numerous leucocytes.

FECES: April 15.—Light yellow fluid stool, with granular sediment. Offensive odor. Few epithelial cells and leucocytes. No red cells. Cercomanos intestinalis numerous.

Treatment and Result.—From the history and from the enlarged liver, malignant disease of the stomach, with probably a secondary involvement of the former organ, was suspected in spite of the patient's age (18 years). With the possibility of tuberculous peritonitis in view, Dr. A. A. Snyder opened the abdomen and discovered very minute miliary tubercles on the small intestine, though no active inflammatory condition existed. Death occurred shortly afterward. The extreme tenderness over the liver, especially in the epigastric region, already mentioned, must have been due to the large gastric ulcer disclosed at the autopsy, the details of which follow. Tuberculous ulcer of the stomach was not suspected, though the history suggested a possible ulcer.

AUTOPSY—MACROSCOPIC EXAMINATION.

General Appearance.—Small negro girl. Much emaciated. Bones small and symmetrical. Marked depression of supraclavicular and infraclavicular regions, not so marked in intercostal spaces. Breasts relatively well developed. No skin lesions.

Respiratory System.—Larynx normal. Lungs collapsed on opening thoracic cavity. They are of a pinkish-white color and mottled with anthracotic pigment, soft, crepitant and float in water. On section, moderately moist, reddish-pink color and pigmented. Bronchi contain pinkish frothy material. Neither lung shows any adhesions. The pleura is a light pink color and smooth throughout; no adhesions. Bronchial glands not enlarged and show no gross evidence of tuberculosis.

Circulatory System.—Heart small, weighing 145 grams. Normal position. Brownish-red color and flabby texture. Aortic and pulmonary valves normal. The tricuspid leaflets thickened and show areas of opacity. Anterior leaflet of mitral valve thickened, yellowish white and quite hard. All cavities contain dark clotted blood. Pericardium normal. No atheroma of aorta.

Lymph Glands.—The retroperitoneal glands were much enlarged, forming a fusiform tumor along the left of the spinal column for about six inches, the upper pole lying beneath the left lobe of the liver. These glands are conglomerate, soft, of a greenish-yellow color, and completely necrotic from cheesy degeneration. The centers of some of them have undergone liquefaction. The glands along the lesser curvature of the stomach, portal vein, behind the stomach, and around the head of the pancreas are also enlarged and similarly affected. The mesenteric glands are but slightly enlarged and are congested. Near the intestinal ulcer is one the size of a pea. Superficial glands are not enlarged.

Spleen.—Bright red color, dry, firm and greasy on section. Usual markings replaced by lobular like structure. Weight, 130 grams. Iodin reaction for amyloid.

Thyroid Gland.—Normal.

Liver.—Ten cm. below costal arch in midaxillary line; 12 cm. below ensiform. On left extends to junction of midclavicular line and ninth costal cartilage. Upper relations normal. Weight, 1,800 grams. Firm and slightly nodular to the touch. Reddish green color. On section, dry, firm and greasy. Iodin reaction for amyloid

positive. The nodules beneath the capsule are small, yellowish white and soft, and similar areas are seen deeper in the organ.

Pancreas.—Normal in size and situation. Head firmly bound down by adhesions with enlarged glands. On section head shows areas of cheesy degeneration. None found in tail.

Kidneys.—Normal position. Pale, firm and greasy. Weight of right, 140 grams; left, 160 grams.

Genital Organs.—Uterus small and retroflexed by adhesions. Right ovary prolapsed into cul-de-sac; left one firmly adherent. Organs normal.

ALIMENTARY TRACT.

Peritoneum.—Parietal layer pinkish-white, smooth, moist and glistening; 200 c.c. cloudy reddish fluid in cavity. Adhesions in region of cecum and pelvis. Omentum ample, contains normal amount of fat, bile-stained in region of gall bladder.

Intestines.—The small intestine is a pale pink color. From the pylorus to the cecum, beneath the serous coat, are numerous minute grayish-white, raised points, giving a granular appearance to the gut. About midway, within the lumen, is a circular ulcer 2 cm. wide. Ulcer is undermined with ragged edges, which show some thickening. An enlarged gland is present just without at the mesenteric attachment, but not communicating. Bowel is congested in region of ulcer. Large intestine collapsed and no lesions present either without or within.

Stomach.—Organ small and normally situated. No adhesions except at cardia and along lesser curvature. Dissection of this region shows three large caseous lymphatic glands, the largest 4 by 2 cm.; one situated close to the esophagus, one about the middle of the lesser curvature, and the other between these two. The gland in relation with the esophagus has no connection with the stomach wall, but the other two are intimately fused with what proves to be the base of a large ulcer on the inside of the stomach. The outer gland shows calcareous areas, and all are caseous. Several small congested glands are seen around the cardiac orifice, but these are not caseous as are the larger ones. On opening the stomach a large single ulcer is seen in the cardiac end, extending nearly around the esophageal opening and to the middle of the lesser curvature, its outer extent corresponding to the situation of the outer large lymphatic gland. It is covered with a yellowish-white mucoid material. The dimensions of the ulcer are: Length, 9 cm.; width, 4.5 cm. Its edges are irregular, undermined, much thickened, very firm and pale. The floor is cribriform and of varying thickness, measuring at one point 4 mm., at another 1 mm., and at one point only the serous coat is present. Tubercles are not evident in the floor. Dissection from without in, opposite the middle lymphatic gland, just beneath the superficial portion of the floor, shows a calcareous area 2 mm. in diameter, surrounded by a circular zone of pearly white tissue. The mucosa elsewhere shows no ulcers. The lymphatics on the serous coat in the vicinity of the caseous glands and elsewhere show no tubercles.

Esophagus.—Normal.

AUTOPSY—HISTOLOGICAL EXAMINATION.

Liver.—Extreme amyloid degeneration. Tubercles, with giant cells. Round cell proliferation in portal tracts and a high grade of fatty degeneration.

Pancreas.—Section from head shows caseation, but no giant cells. Areas of round cell proliferation in lobules.

Kidneys.—Extensive degeneration of epithelium of convoluted tubules. Marked amyloid degeneration, principally in the tufts. Areas of round cell proliferation throughout. Increase of connective tissue between tubules in pyramidal portion.

Spleen.—Practically all amyloid. Here and there are seen remains of Malpighian bodies with dilated and congested vessels. No tubercles seen.

Intestine.—Sections from ulcer and contiguous tissue show numerous tuberculous areas, varying in size. The centers of these are caseous, with outer zones of lymphoid and epithelioid cells. The most conspicuous condition is a hyperplasia of the connective tissue elements in the submucosa, with areas of adipose tissue and numerous dilated and congested vessels. Giant cells are present, but only occasionally seen. The vessel walls are thickened and show a hyaline degeneration. In places the muscular coat has been infiltrated, and in some places entirely replaced, by the tuberculous process, the latter extending to the peritoneal coat. The base of the ulcer shows superficial necrosis, beneath which is connective tissue, infiltrated with lymphoid and epithelioid cells. Edges of ulcer show chronic thickening. Mucosa of intestine elsewhere shows atrophy of epithelial elements.

Stomach.—Our studies here included examination of section from various portions of the ulcer and stomach wall. The base of the ulcer is for the most part composed of the outer longitudinal muscular coat, though in places there is only the thickened serosa. The gastric surface shows superficial necrosis. Beneath this zone of necrosis is a chronic hyperplasia of the connective tissue, with many lymphoid and epithelioid cells. In some places the muscular coat is entirely replaced by this process. The serous coat is much thickened and infiltrated with lymphoid cells, which are seen in longitudinal columns. Some of the vessels are completely organized and all show thickened walls with a hyaline degeneration. Direct communication can be traced to one of the lymphatic glands through the serous coat. The edges show atrophy, distortion and degeneration of the gland tubules, with a marked proliferation of the interglandular connective tissue. Near the esophagus are areas showing dense aggregations of lymphoid cells with necrotic centers. One of these extends to the surface. No giant cells are seen in any of the stomach sections examined. Tubercle bacilli in small numbers (usually in groups of two or three) are found in the edge of the ulcer. The organ in other portions, but for an atrophy of the mucosa, is normal.

Lungs.—Larger vessels congested and mild grade of capillary congestion. Anthracosis. Alveoli dilated in places, but contain no exudate, cells or débris.

Myocardium.—Normal.

Thyroid Gland.—Normal.

Lymph Glands.—Sections of various lymphatic glands show them to be uniformly necrotic, with occasionally a narrow rim of the gland tissue. No giant cells are seen in any of the glands.

ANATOMIC DIAGNOSIS.

Single tuberculous ulceration of the stomach and intestine; tuberculosis of the abdominal lymphatic glands, liver and pancreas. Amyloid degeneration of spleen, liver and kidneys. Tuberculous peritonitis, involving the visceral layer of the small intestine.

The point of greatest interest in our case is the healthy condition of the lungs, which is most unusual when there is tuberculous ulcer of the stomach. We have found but six similar instances, abstracts of which follow:

CASE 1.—Reported by Besnier.[8] Man, 57 years old, sick three months, greatly emaciated, lower extremities edematous. Nothing found in thorax or abdomen to explain cachexia. The only symptoms: Diarrhea, loss of appetite and vomiting. Autopsy showed tuberculosis of the abdominal glands, with one large gland ad-

8. Bull. Soc. anat. de Paris, March, 1867, p. 97.

herent to the posterior wall of the stomach, this gland having suppurated and perforated into the organ.

CASE 2.—Reported by Paulicki.[9] Man, 41 years old, presenting symptoms of anorexia, repeated bloody vomiting, finally death from peritonitis. Autopsy showed several ulcers near the pylorus, varying in size, the largest, one and one-half inches long, situated on the anterior surface of the stomach, had perforated. Tuberculosis of the glands along the lesser curvature and of the mesenteric glands. Ulcers in the intestines. Few miliary granulations in liver and kidneys. No tuberculosis of the lungs.

CASE 3.—Reported by Hattute.[10] Man, 47 years old, complained of having vomited his food for about eight years. After each meal there was acute pain in the stomach. There would be distension and in from ten to twenty minutes, very rarely at the end of an hour, vomiting would occur. This happened even after small amounts of water were taken. There was marked tenderness over the epigastrium. No melena. Autopsy showed tuberculous peritonitis, marked pyloric obstruction due to a circular mass of granulations similar to those on the peritoneum. Mesenteric and bronchial glands tuberculous. Some pleural adhesions. Lungs healthy.

CASE 4.—Reported by Lava.[11] Man, 26 years old, history of gastric catarrh for three years. Epigastric pain, vomiting and diarrhea. Abdomen became tender to pressure. A painful mass felt in the right hypochondrium. The diagnosis of pyloric stenosis, with probably gastric ulcer was made. Symptoms of acute peritonitis developed and death occurred in twenty-four hours. Autopsy showed a circular ulcer found in the pyloric region which had perforated. Old adhesions between the stomach and intestines. Pyloric glands very large and caseous. Microscopic examination showed typical tubercular structure. No trace of tuberculous process in the lungs or in other organs.

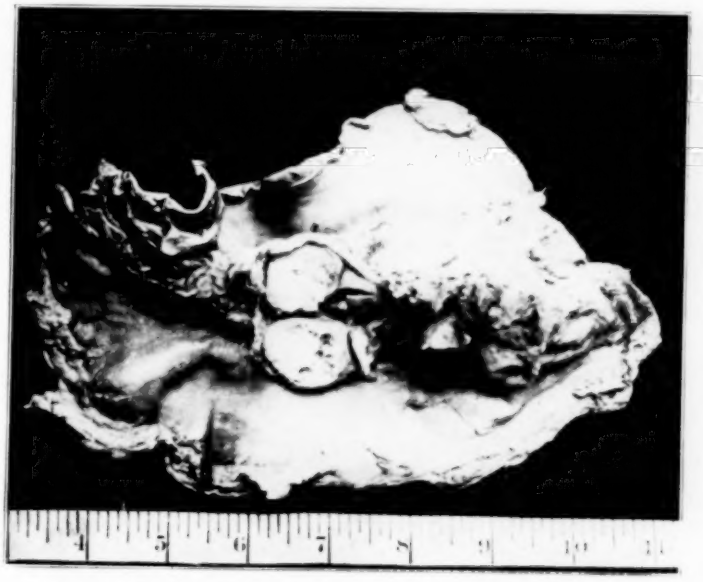
This case was most remarkable in that there was no tuberculous process in other organs.

CASE 5.—Reported by Orlandi.[12] Man, 26 years old, suffered from the age of 14 to 17 with intestinal parasites. Some years later, dyspeptic symptoms developed, at first stomachic, later intestinal. These phenomena grew progressively worse, with rapid emaciation, finally ending in death. Autopsy showed an annular ulcer surrounding and obstructing the pylorus. Neighboring lymphatic glands were greatly enlarged and caseous. Histologic examination proved the ulcer to be tuberculous. There was no trace of tuberculosis of the lungs or of any other lymphatic glands. This was apparently a primary lesion of the stomach.

CASE 6.—Reported by Margarucci.[13]. Man, 65 years old, delicate from infancy, had malarial fever and syphilis. Some years earlier he began to vomit after eating, at first without pain. For six years he vomited five or six times a day, sometimes immediately after taking food, more often several hours after. He then had a respite of five months, during which time the digestion was simply labored. The trouble then reappeared and was variable for three years. Soon in addition to vomiting, severe epigastric pain was added, and the vomitus had the appearance of coffee grounds. The stomach became more and more irritable and emaciation rapidly ensued. He never had any cough or fever. There was constipation later, followed by diarrhea. The abdomen was retracted, and marked intestinal peristalsis was visible. Below the xyphoid, deep pressure caused pain

9. Berl. klin. Wchnschr., August, 1867, p. 349.
10. Gaz. d. Hôp., 1874, p. 859.
11. Gaz. med. di Torino, 1893, p. 915.
12. Gaz. med. di Torino, 1893, p. 33.
13. Policlinico, Rome, 1898, p. 75. Sezione Chirurgica.

Internal view of stomach showing ulcer. Organ opened on greater curvature.



External view of lesser curvature of stomach showing caseous glands.

and an ill-defined resistant surface could be felt moving slightly with respiration. Clinical tests indicated pyloric obstruction. Gastroenterostomy and enteroplasty were done, but death occurred two days later. Autopsy showed multiple stenoses of the intestine and stenosis of the pylorus, due to an ulcer which was histologically shown to be tuberculous. The lungs were free from tuberculosis.

The first four cases were cited by Arloing,[3] the last two by Ricard and Chevrier.[4]

SUMMARY.

Our studies show a case of tuberculous infection of the digestive tract, as evidenced by the limitation of the process to the stomach, intestine, liver, pancreas and lymphatic structures draining these organs.

There existed a large single tuberculous ulcer of the stomach, with no involvement of other parts of the organ. This ulcer possessed the usual characteristics of a tuberculous lesion—ragged, thickened, undermined edges and cribriform floor. This was confirmed by histologic examination and the finding of tubercle bacilli in the tissue.

The connective tissue hyperplasia, absence of giant cells and paucity of bacilli in the tissue, speak for an attenuated infective process.

The route of infection seems to have been through the lymphatic system of the gastrointestinal tract. Pulmonary origin has been absolutely excluded by the absence of any tuberculous lesions in the lungs or bronchial glands. This fact was determined with great care, both macroscopically and microscopically.

As to whether the primary seat of infection was the ulcer in the stomach, from which the abdominal lymphatics became infected, or whether the lymphatic glands infected the gastric wall by contiguity, we are unable to say, but the latter seems the more probable.

1315 New Hampshire Avenue.

SEROTHERAPY OF EPIDEMIC CEREBROSPINAL MENINGITIS.

REPORT OF TWELVE CASES.

W. S. CHASE, M.D., AND M. L. HUNT, M.D.
AKRON, OHIO.

In the months of April, May and June, 1907, there were reported to the Health Officer of Akron 22 cases of epidemic cerebrospinal meningitis. The first case came down April 28, the most of them occurring in May and June. The last one was admitted to the hospital September 11, having first shown symptoms six days before.

Four of the patients, strong, healthy young men, were employed at one of the local rubber factories. In no other instance could there be shown any possibility of communication by contact. In fact, a striking feature of the epidemic was the occurrence, at the same time, in widely separated districts of the city, of single cases.

Twelve of the cases were treated at the Akron City Hospital. Of these, 3 of the patients died and 9 recovered, a mortality of 25 per cent. Of the cases outside, one patient recovered and 9 died, a mortality of 90 per cent. All of those treated at the hospital received the Flexner antiserum. Those treated outside did not. The diagnosis of the case of the one outside patient, who recovered, was not confirmed by lumbar puncture and presented atypical symptoms.

While realizing the ease with which the *post hoc* may blossom into the *propter hoc*, when the treatment of any disease is concerned, it seems to us that the striking difference in the mortality rate of these two sets of cases is more than enough to warrant a further and wider trial of the Flexner antiserum.

At the time of the outbreak in Akron the Flexner antiserum had been tried in a few cases at Castalia, Ohio. A supply of this serum was sent to Akron by Dr. Flexner from the Rockefeller Institute of New York, with the understanding that the necessary bacteriologic examinations be made in each case. In order that this might be done under the most favorable conditions, it was decided that the serum should be administered only to patients received at the Akron City Hospital. That fact was communicated to the physicians of the city, and a committee of three physicians from the medical staff of the hospital was appointed to see in consultation the cases of epidemic spinal meningitis admitted, and to have general supervision of the serum administration and of the bac-

teriologic work. That committee consisted of Drs. A. A. Kohler, C. E. Held, and W. S. Chase. They were assisted in their work by Drs. M. L. Hunt and G. M. Logan, the hospital internes.

The diagnosis was made in no case on the clinical signs alone, but these were supplemented, in each instance, by microscopic and culture tests of the spinal fluid withdrawn by lumbar puncture. A puncture was done under aseptic precautions whenever clinical evidence warranted it and as soon as possible after the patient's admission.

In the first few cases the antiserum was not administered until after a microscopic examination of the withdrawn fluid had been made showing the presence of Weichselbaum's *Diplococcus intracellularis*. Later on, when the clinical evidence seemed positive, the injection of the serum was made at the time of the first puncture; but in all cases the clinical evidence was corroborated by the subsequent microscopic findings.

As all the patients were more or less wildly delirious, it was found advisable to perform lumbar puncture, in almost every instance, under general anesthesia. For that purpose chloroform was used. An ordinary aspirating needle was employed, about 10 cm. in length, and, with the patient on his side, with thighs flexed on the abdomen and shoulders brought forward, the needle was inserted about 1 cm. beyond the median line, between the third and fourth lumbar vertebræ. This level is crossed by a line connecting the iliac crests.

The only medication any of the patients received, aside from the injections of serum, was an occasional hypodermic injection of morphin combined with hydrobromate of hyoscin, when delirium and restlessness were pronounced. This was not given to all the patients.

The following synopses taken from the clinical charts while the patients were in the hospital show the progress of each case from day to day:

CASE 1.—*Patient.*—V. H., aged 9, schoolgirl. Referred by Dr. L. R. C. Eberhard. Admitted April 30, 1907, at 9:30 p. m.

History.—Patient first complained of pain in the stomach and legs aching April 28; vomited early in the morning and frequently during the day. She became unconscious about 7 p. m. April 28 and was restless and noisy most of the night. The same conditions prevailed on Tuesday morning, when the family noticed retraction of the head and rigidity of the neck. Tuesday evening patient became worse and more restless, throwing and tossing herself about and screaming. Sordes on tongue, lips and teeth.

Condition on Admission.—Temperature 99.6 F., pulse 100, respiration 24. Unconscious; restless and screaming, especially if touched; pupils moderately dilated but fixed; no nystagmus; plantar, patellar and abdominal reflexes absent; Kernig sign positive; herpes labialis; neck rigidity marked and opisthotonus; sphincters intact.

May 1 and 2: Condition unchanged.

May 2: Temperature 99.6; pulse 100. Lumbar puncture at 9 a. m. yielded 30 c.c. of opalescent fluid; examination showed diplococci, extra- and intra-cellular.

May 3: Condition practically the same as on preceding day, except for loss of sphincter control.

May 4: Condition no better. On lumbar puncture at 10 a. m. 10 c.c. of fluid withdrawn and 10 c.c. of antiserum injected. Convulsions involving left side and face from 10:40 until midnight; chloroform necessary to control; conscious at 8 p. m.; reflexes absent; Kernig present; neck rigid; nystagmus.

May 5: Temperature normal part of the day; pulse 116 to 120. Condition improved; called for milk and water; restless at intervals.

May 7: Temperature and pulse normal. Restless and noisy at times.

May 8: Temperature began to rise and reached 103.6 F.

May 9: Complained of frontal headache. On puncture 30 c.c. of fluid withdrawn; 7.5 c.c. of serum injected. Vomited supper. Reflexes absent.

May 10 and 11: Temperature at or near normal all day; child much improved; not very restless.

May 12: Temperature rose to 104.2; pulse 140. Restless and noisy in the evening; headache. On puncture at 9 p. m. 60 c.c. of fluid withdrawn; 7.5 c.c. of serum injected; stained specimens failed to show diplococci.

May 13 and 14: Temperature at or near normal; greatly improved.

May 15: Temperature 99 to 104 F.; pulse 94 to 136. Puncture at 8 p. m. yielded 20 c.c. of fluid; no serum injected.

May 16: Child not so well; vomited during the day; severe headache and restless.

May 17: Very irritable; noisy and restless; headache; slight abdominal reflex present.

May 19: Knee and plantar reflexes present for first time; Kernig positive. Rational; irritable, but more quiet than usual; calls for food.

May 20 to 25: No marked change, except for some pain in right leg along course of femoral nerve.

May 25: At 10 a. m. 90 c.c. of fluid withdrawn by puncture; 20 c.c. of serum injected; stain negative. At 8 p. m. marked urticaria.

May 26: Temperature normal most of the day; quiet and felt much better; reflexes all present; pain in right leg better; mentality good; involuntary urination. Continued thus for two days.

May 28 to June 3: Temperature ranged between 99 and 103 F.

June 3: Very restless, shouting and crying. At 10 p. m. puncture yielded 75 c.c. of fluid; 15 c.c. of serum injected.

June 4 to 14: Temperature was practically normal; general condition good; rational and moderately quiet most of the time. Reflexes all present and normal; Kernig absent; neck not rigid; perfect function of all parts; no headache; appetite capricious.

June 14: Patient became very restless and noisy. Severe pain in back, leg and abdomen; face flushed; urine and feces involuntary; reflexes all normal; Kernig absent; no neck rigidity.

June 15: At 2 p. m. puncture yielded 75 c.c. of fluid; stain positive; 22.5 c.c. of serum injected. Vomited at midnight.

June 16: Vomited in the morning; refused breakfast; complained somewhat of frontal headache.

June 17: Better to-day; no pain; appetite good.

June 26: Condition good. Reflexes all present and normal; Kernig absent; neck not rigid; no unfavorable sequelæ apparent. Sitting up in bed did not disturb her; less irritable than at any time. Temperature normal from this date on.

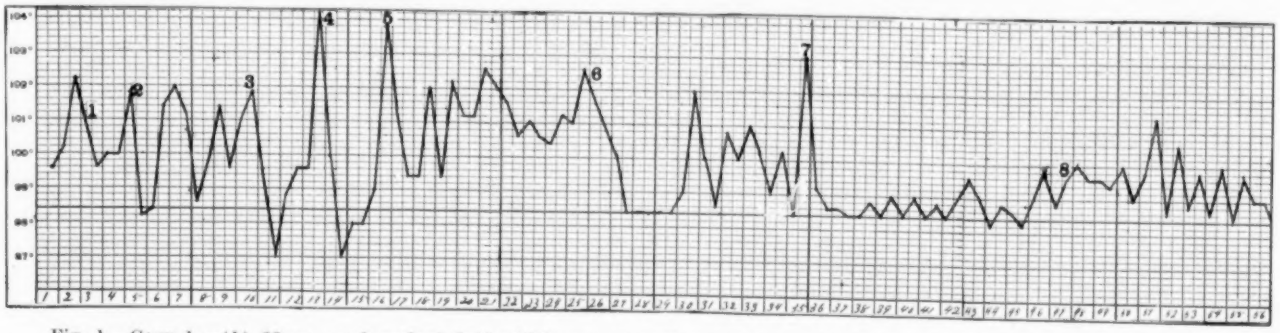


Fig. 1.—Case 1.—(1) 30 c.c. cerebrospinal fluid withdrawn; no antiserum given. (2) 10 c.c. cerebrospinal fluid withdrawn and 10 c.c. antiserum injected. (3) 30 c.c. cerebrospinal fluid withdrawn and 7.5 c.c. antiserum injected. (4) 60 c.c. cerebrospinal fluid withdrawn and 7.5 c.c. antiserum injected. (5) 20 c.c. cerebrospinal fluid withdrawn and no antiserum injected. (6) 90 c.c. cerebrospinal fluid withdrawn and 20 c.c. antiserum injected. (7) 75 c.c. cerebrospinal fluid withdrawn and 15 c.c. antiserum injected. (8) 75 c.c. cerebrospinal fluid withdrawn and 22.5 c.c. antiserum injected.

She began to walk, and July 4 commenced to develop a kyphosis; no angular deformity; spine mobile, not painful; only noticeable when standing; involved the whole length of spine. Gymnastics and massage were instituted and used until July 14, when she was put in plaster jacket. The child made a good recovery, and left the hospital Aug. 6, 1907, 96 days after admission. She has been back to the hospital several times since, and is bright mentally and in good condition.

The clinical symptoms in this case were typical, and it would have been almost impossible for one to make an error in diagnosis depending on them alone. This was the first case in which the Flexner antiserum was used. It was brought from Cleveland by Dr. Ladd, who saw the patient in consultation. There was nothing then to govern the dosage in human beings, but the largest dose which had been given up to that time (10 c.c.) was administered May 4, care being taken to inject no more in volume than the fluid withdrawn. This precaution was afterward disregarded as unnecessary, and the dosage was very materially increased. In spite of the precaution, however, the first injection was followed by convulsions. These were not excited by large amounts later on and did not appear spontaneously. It is, therefore, probable that the association was accidental.

As Flexner and Jobling have pointed out in their article which appeared in the January (1908) number of *Experimental Medicine*, where the first record of the treatment of human beings with this serum is given, it is very difficult to assign a definite effect to the serum in a case so protracted as this. These facts, however, stand out in the history: Within 24 hours following each injection of serum the patient's mental condition was materially improved and the temperature dropped to normal or nearly normal. That improvement was not noticed following a lumbar puncture on May 15, when no serum was injected. Neither was there a fall of temperature nor an improvement in the mental condition when the exacerbations, which occurred periodically throughout the course of the disease, were allowed to go without a lumbar puncture or an injection of serum.

CASE 2.—*Patient.*—H. R., aged 17; rubber worker. Treated by Dr. George Rankin. Admitted May 9, 1907, at 12 m.

History.—Patient was perfectly well on May 8 and worked, but returned home, not feeling well, complaining of headache; was restless the greater part of the night and did not sleep well; vomited during the night, and became unconscious a few hours before admission to the hospital. He also complained of pain in extremities and cramps in legs.

Condition on Admission.—Temperature 101.6 F.; at 11 p. m. temperature was 105.4 F. Pulse 90; pulseless after 2 p. m. Respiration 40; gradually increased to 70 at 10 p. m. Comatose. Pupils: Left contracted, right dilated; did not react to light. Slight nystagmus; plantar, patellar and abdominal reflexes absent; Kernig sign present; no herpes; neck rigid; loss of sphincter control. On

puncture at 3 p. m. 60 c.c. of opalescent fluid withdrawn; stain positive. A second puncture at 11 p. m. gave 60 c.c. of fluid. The antiserum had to be obtained from Cleveland, and none was received until 11 p. m., when 10 c.c. were administered. At that time patient was practically pulseless.

May 10: Temperature at 3 a. m., 106.8 F.; pulseless. Temperature at 5 a. m., 107.2 F.; Cheyne-Stokes respiration; cyanosed; vomited frequently after 12 m. Died at 5:42 a. m.

CASE 3.—*Patient.*—B. S., aged 19; rubber worker. Treated by Dr. W. S. Chase. Admitted May 14, 1907, at 6 a. m.

History.—Patient was well up to May 12, two days before admission to the hospital, when he went to his room complaining of headache. He also had a chill. He was in bed all day May 13; headache worse; vomited and was nauseated; did not eat anything all day. He became unconscious about the time he was moved from his room to start for the hospital.

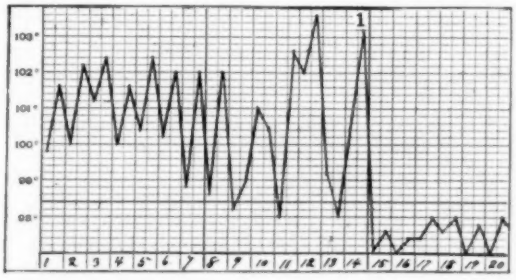


Fig. 2.—CASE 3.—(1) 60 c.c. cerebrospinal fluid withdrawn and 20 c.c. antiserum injected.

Condition on Admission.—Temperature 99 F.; at midnight temperature was 101.6 F. Pulse 56; 9 a. m. to 12 m. pulseless; midnight, 86; markedly cyanosed. Respiration from 32 to 34 and irregular at midnight. Unconscious and wildly delirious; pupils normal; no nystagmus; plantar, patellar and abdominal reflexes absent; Kernig sign positive; no herpes; neck rigid; sphincters intact; urine showed albumin.

May 15: No better. Temperature at 3 p. m., 102.4 F.; pulse 80; respiration 30. Delirious; neck and spine rigid; talking constantly; gets out of bed; passed a round worm 11 inches long.

May 16: No better. At midnight temperature 102.4 F.; pulse 120; respiration 26. Involuntary urination. Puncture attempted, but not successful.

May 17: No better. At 6 p. m. temperature 101.6 F.; pulse 110; respiration 28. Delirious and restless all day. Coughing; face flushed at times; passed a round worm 9 inches long.

May 18: No better. At 3 p. m. temperature 102.4 F.; pulse 98; respiration 28. Delirious and restless.

May 19: Highest temperature 102.2 F.; pulse 108 and weak; respiration 24. Not quite so restless; involuntary urination. Condition continued practically unchanged until May 22, when temperature was normal all day; passed two round worms. Temperature also normal on May 26, but ranged between 99 and 103.6 F. on May 23, 24, 25 and 27.

May 27: Physical examination showed neck rigid; slight return of plantar and patellar reflexes; abdominal reflex absent. Lumbar puncture at 10 a. m., under local anesthesia, yielded 60 c.c. of slightly cloudy fluid; 20 c.c. of antiserum injected; stain showed diplococci.

May 28: Temperature normal all day; patient resting and eating well; apparently in good condition.

May 29: Temperature normal all day; neck rigidity less. Patient continued to improve until June 6, the twenty-fourth day of the disease, when he was able to walk out of the hospital.

CASE 4.—*Patient.*—F. N., aged 32; laborer. Treated by Drs. W. S. Chase and Charles E. Held. Admitted May 16, 1907, at 4:30 p. m.

History.—Patient, who was a strong, hearty man, had always been well. He worked on May 15, but complained of severe headache during the latter part of the day and in the evening. He went to his family physician, who prescribed for his pain, but without relief. On the morning of the 16th he was no better and still complained of severe pain in his head and neck, but had no fever. Morphin, in ½ gr. doses hypodermatically, did not relieve him. A little later he became delirious. Muscular rigidity was marked.

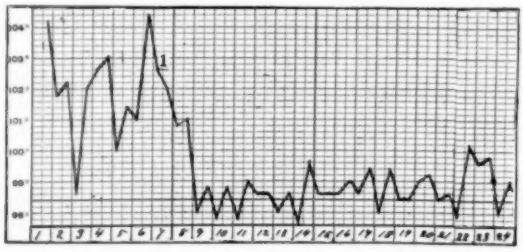


Fig. 3.—CASE 4.—(1) 90 c.c. cerebrospinal fluid withdrawn and 25 c.c. antiserum injected.

Condition on Admission.—Temperature 104.2 F.; pulse 124; respiration 30. Conscious at times only; delirious and restless; pupils normal; plantar, patellar and abdominal reflexes absent; Kernig sign positive; no herpes; no neck rigidity; sphincters intact; no nystagmus.

May 17: Temperature at 6 a. m. 101.8 F.; 9 p. m. 102.2 F. Condition slightly improved; conscious at times; noisy and restless; severe pain in head. Urine showed albumin and casts. Put in restraint. Puncture unsuccessful. Pulse weak at times—128 and 134.

May 18: Temperature at 6 a. m. 98.6 F.; pulse 96. At 12 m. temperature 102 F.; pulse 100. Severe pain in head; delirious and noisy.

May 19: Temperature at 6 a. m. 102.6 F.; pulse 116. At 9 p. m. temperature 103 F.; pulse 130. Pain in head severe; delirious and noisy most of the time; hallucinations; respiration 34 to 48 and irregular.

May 20: Temperature at 6 a. m. 100 F.; pulse 110. At 9 p. m. temperature 101.2 F.; pulse 110. Condition the same as on preceding day.

May 21: Temperature at 6 a. m. 101 F.; pulse 106. At 9 p. m. temperature 104.4 F.; pulse 110. Condition not much changed; delirious; restless; talking and hiccoughing.

May 22: Temperature at 6 a. m. 102.6 F.; pulse 98. At 12 m. temperature 102 F.; pulse 98. On puncture with a long needle 90 c.c. of fluid withdrawn; stain showed diplococci; 25 c.c. of serum injected. Pulse irregular.

May 23: Temperature at 6 a. m. 100.8 F.; pulse 96. At 12 m. temperature 98 F.; pulse 90. Patient much improved; conscious and resting quietly all day.

May 24: Temperature normal; condition good, except pain in right arm at times. Urine showed trace of albumin; few casts. Appetite good.

May 25: Temperature normal; no pain; felt well; reflexes all present; Kernig absent; neck slightly rigid.

May 26 to 31: Continued to improve; sat up in bed. Reflexes all present; no pain.

June 1 to 5: Furuncle in right axilla incised. Sat up every day; no pain. Temperature normal.

June 6: Temperature at 6 a. m. 98 F.; pulse 98. At 9 p. m. temperature 100.2 F.; pulse 94. Severe pain in back and legs; unable to move legs; reflexes in legs and feet can not be elicited—rigid; pain and tactile sensation undisturbed.

June 7: Temperature at 6 a. m. 99.6 F.; pulse 114. At 12 m. temperature 99.4 F.; pulse 104. Extremities less painful, except when moved; marked tenderness over large nerve trunks; pain in lower jaw on movement.

June 8: Temperature at 6 a. m. 100 F.; pulse 106. At 9 p. m. temperature 99.4 F.; pulse 104. Felt better; less pain and tenderness not marked. Leucocyte count 22,600.

June 9: Temperature normal; much better; moved legs without pain.

June 10 to 15: Neuritis continued to improve. Discharged, feeling well, June 15, thirty-one days after admission.

Cases 3 and 4 were both marked by a very severe onset. In Case 3 the patient showed extreme cyanosis an hour after admission and was pulseless at the wrist. Diffusible stimulants and oxygen were used freely. These cases are of special interest when compared with some of the others, in that the injections of antiserum were made rather late in the disease. So far as two cases of the same disease can resemble each other they were running the same kind of course. In Case 3 a successful puncture was made on the fifteenth day of the disease. Within 24 hours after an injection of 20 c.c. of antiserum the temperature was normal and the mental condition greatly improved. In Case 4 puncture and injection were performed on the tenth day. Within 24 hours the patient's temperature was normal and he had passed from a period of wild delirium to one of complete consciousness and quiet. It is noteworthy to observe, also, that both patients, save for the neuritis in Case 4, made speedy and uneventful recoveries.

CASE 5.—*Patient.*—B. K., aged 15; factory girl. Treated by Dr. L. R. C. Eberhard. Admitted May 16, 1907, at 9 a. m.

History.—Patient had some headache May 15. It was not very severe, but she noticed that she was more nervous than usual. She slept well that night and was conscious on the morning of May 16. Still complained of headache, which was more severe than on the day before. She refused breakfast. Her mother gave her an enema, thinking it would relieve her pain. After this the mother went downstairs and returned in about twenty minutes to find the patient unconscious. The family physician was called and found the patient throwing her-

self around and tossing about on the bed. Rigidity was very marked. She was sent to the hospital at once.

Condition on Admission.—Temperature 103.6 F.; pulse 84 and irregular; respiration 34; comatose; pupils dilated, but reacted; nystagmus; plantar, patellar and abdominal reflexes absent; Kernig sign positive; no herpes; neck rigid; sphincters intact; urine showed albumin. Lumbar puncture gave 45 c.c. of opalescent fluid; diplococci present; 15 c.c. of antiserum injected.

May 17: Temperature at 6 a. m. 99.8 F.; pulse 70; respiration 24. At 12 m. temperature 102.6 F.; pulse 100; respiration 26. Conscious; noisy and restless at times and complained of severe headache.

May 18: Temperature at 6 a. m. 101.6 F.; pulse 94; respiration 20. At 12 m. temperature 100.2 F.; pulse 82; respiration 24. Semiconscious; knee and plantar reflexes present; abdominal reflex absent; Kernig sign present; pain in head severe; noisy at times; involuntary urination.

May 19: Temperature at 6 a. m. 100.8 F.; pulse 90; respiration 20. At 12 m. temperature 102 F.; pulse 96; respiration 22. Semiconscious, but rational when spoken to; herpes labialis appearing; knee and plantar reflexes diminished; abdominal reflex absent; internal squint of both eyes—more pronounced in right. On puncture there was withdrawn 4.5 c.c. of cloudy fluid; 5 c.c. of serum injected.

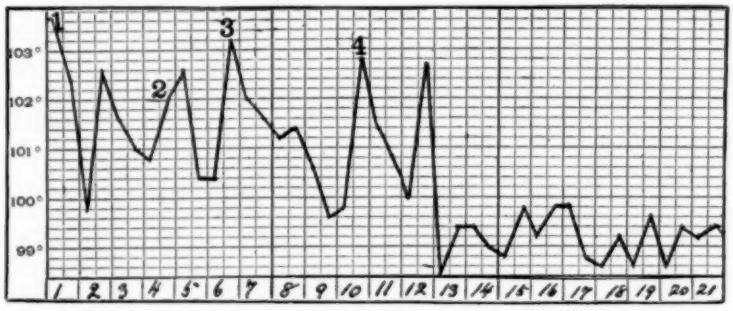


Fig. 4.—Case 5.—(1) 45 c.c. cerebrospinal fluid withdrawn and 15 c.c. antiserum injected. (2) 45 c.c. cerebrospinal fluid withdrawn and 5 c.c. antiserum injected. (3) 4 c.c. cerebrospinal fluid withdrawn and 3.5 c.c. antiserum injected. (4) 75 c.c. cerebrospinal fluid withdrawn and 20 c.c. antiserum injected.

May 20: Temperature 100.8 to 102.6 F.; pulse 106 to 120. About same condition as on day preceding; strabismus not quite so marked; rational when spoken to; unable to move arms; headache severe.

May 21: Temperature in the morning 103.2 F. Puncture yielded 4 c.c. of fluid; 3.5 c.c. of serum injected; stain positive.

May 22: Very irritable; headache severe; pain all over on being moved; herpes on ear; squint not so marked; pupils dilated, react; knee and plantar reflexes present; transient hyperemic areas on abdomen.

May 23: Restless and noisy; severe pain in left leg; unable to move left arm and leg; headache constant.

May 24: Temperature at 6 a. m. 100.6 F.; pulse 120. At 12 m. temperature 102 F.; pulse 100. Semiconscious; irritable; pain in head, left arm and leg; right arm all right.

May 25: Condition same as on preceding day, except decubitus of left heel and elbow; tactile and pain sensations normal on left side; 75 c.c. of fluid withdrawn by puncture and 20 c.c. of serum injected; stain failed to show diplococci; involuntary urination and bowel movements.

May 26: Temperature at 6 a. m. 101.4 F.; pulse 108. At 12 m. temperature 100.6 F.; pulse 120. Patient better; complains of pain in head at times and is restless and noisy; rational when spoken to; reflexes same as on preceding day.

May 27: Temperature at 6 a. m. 100 F.; pulse 104. At 12 m. temperature 102.6 F.; respiration 26. Reflexes all present; conscious; neck rigid; Kernig sign present; pain in head, arms and legs on movement.

May 28: Temperature 98.4 to 99.4 F. Urticaria on knees and elbows.

May 30: Patient improved. Some headache at times; urine normal; no involuntary urination; knee and plantar reflexes normal; abdominal reflex absent; Kernig sign present; neck less rigid; left arm and leg well; sphincters normal. From this day patient gradually improved, highest rectal temperature being 99.8 F. Her appetite was good and she was free from pain, but she did not gain strength rapidly.

June 8: Kernig sign absent; neck not so rigid; no pain anywhere; felt well, and appetite excellent. She had normal temperature from this date until date of discharge, June 27, being 41 days after admission to the hospital. She was perfectly well in every way, except not as strong as formerly. Patient came to the hospital early in September, feeling all right in every way.

In the light of our present knowledge, it is apparent that the first three injections in this case were entirely too small, especially the second and third. It is uncertain, of course, whether larger doses at these times would have affected the course of the disease, but they should certainly have been given.

CASE 6.—*Patient.*—Z. H., female, aged 17; rubber worker. Treated by Dr. W. S. Chase. Admitted May 19, 1907, at 6 p. m.

History.—Patient had been well, and worked until Saturday noon preceding. She complained somewhat of soreness and aching in the back and legs. At 2 a. m. May 19 she complained of headache and became unconscious about 3 a. m. She was first seen by a physician at 7 a. m. and was reported to have some fever. During the early morning and throughout the day she vomited several times and was unconscious and very restless, continually tossing about, rolling her eyes and head and holding herself in tonic contractures.

Condition on Admission.—Temperature at 6 p. m. 101.6 F.; 99 F. at midnight. Pulse at 6 p. m. 104; 80 at midnight. Respiration at 6 p. m. 28; 18 at midnight. Comatose; pupils equal, moderately dilated and reacted to light; nystagmus; plantar and patellar reflexes present; abdominal absent; Kernig sign present; no herpes; neck rigid; control of anal sphincter lost. Lumbar puncture gave 45 c.c. of opalescent fluid; diplococci present; 15 c.c. of antiserum injected.

May 20: Temperature normal; patient conscious; talked rationally to members of her family at 3 a. m.; some frontal headache.

May 21: Temperature normal; mentality not quite so good; involuntary urination and bowel movements; herpes appearing on lips; hyperemic areas on abdomen. At 9 p. m. 60 c.c. of fluid withdrawn by lumbar puncture; diplococci present; 7.5 c.c. of antiserum injected.

May 22: Temperature at midnight 99.2 F.; pulse 92; respiration 18. Patient in good condition. Died suddenly at 12:30 a. m. No postmortem permitted.

It will be noted from the history that this patient became unconscious at 3 a. m. on May 19. She was seen by a physician at 7 a. m. and admitted to the hospital at 6 p. m. on the same day. She was given 15 c.c. of the antiserum about an hour after admission. At 3 a. m. the next day her temperature was normal. She had passed from a deeply comatose state to one of perfect consciousness and conversed freely with members of her family. The change was so marked and so impressed the members of the family that they thought a miracle had been performed.

The second injection was given on the evening of May 21, not because her general condition did not seem excellent, but because she was slightly duller mentally than on the day before. She was reported in good condition at 11:30 p. m. An hour later the attending nurse heard her breathing heavily, and in five minutes she was dead. An autopsy was not permitted, and death must be put down to one of those accidents liable to occur at any time during the course of a severe infection. We can not connect in any way her sudden death with the second puncture. She took the anesthetic well and was in good condition after coming out from under its influence.

CASE 7.—*Patient.*—H. S., aged 14; school boy. Treated by Dr. A. F. Sippy. Admitted May 22, 1907, at 8 p. m.

History.—Patient had been well and first complained of headache the evening of May 21. On the morning of May 22 he had vomited twice and complained of severe pain in the head. His temperature was 101 F.; pulse normal. At 5 p. m. he became delirious, with pupils dilated and fixed, but no neck rigidity.

Condition on Admission.—Temperature 104 F.; pulse 120; respiration 44; unconscious; comatose; wildly delirious and noisy; pupils dilated and fixed; no nystagmus; plantar, patellar and abdominal reflexes absent; Kernig sign present; no herpes; neck slightly rigid; sphincters intact. On puncture 75 c.c. of opalescent fluid obtained; diplococci present; 15 c.c. of antiserum injected.

May 23: Improved; semiconscious; temperature 100 F.; pulse 80; respiration 26; restless and noisy at times; rational at times and complained of severe headache.

May 24: Temperature at 6 a. m. 101.8 F.; 9 p. m. 99.8 F. Rational all day; vomited once; severe headache at night.

May 25: Temperature at 9 a. m. 102 F.; pulse 66; respiration 26. On puncture 75 c.c. of fluid obtained; 20 c.c. of serum injected. Rational all day. Temperature at 9 p. m. 98.8 F.; pulse 68; respiration 24.

May 26: Improved; temperature normal all day; pain in head less; reflexes all present; neck rigidity less.

May 27: Improved; temperature at 7 p. m. 98 F.; resting well; some pain in head.

May 28: Temperature at 7 p. m. 99.8 F.; resting well; no pain; neck slightly rigid.

May 29: Temperature at 3 p. m. 100.2 F.; normal at 12 m.; no pain.

May 30: Temperature 100 F. at 12 m., 3 p. m. and 6 p. m.; normal at 9 p. m.; appetite better; no pain.

May 31: Temperature at 6 p. m. 99.8 F.

June 1: Temperature at 3 p. m. 99.2 F.
June 2: From this day on temperature was normal.
June 8: On this day, 18 days after admission, patient sat up in bed three hours. Discharged from hospital.

This case, while not of the fulminating type, was certainly severe. Any one seeing the boy at the time of admission to the hospital would surely have been justified in giving a very grave prognosis. This being the seventh case in our series, the attending physician became bold enough to give the boy 15 c.c. of antiserum at the first injection. The symptoms

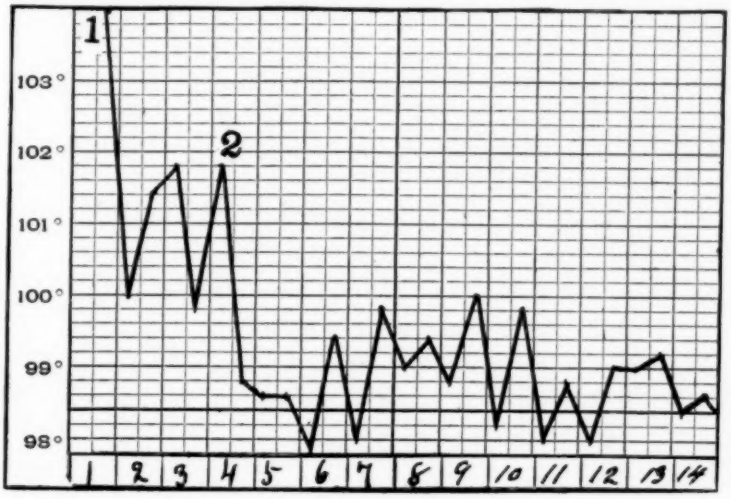


Fig. 5.—Case 7.—(1) 75 c.c. cerebrospinal fluid withdrawn and 15 c.c. of antiserum injected. (2) 75 c.c. cerebrospinal fluid withdrawn and 20 c.c. antiserum injected.

did not abate so rapidly in this case as in some of the others, and on the fourth day of illness the temperature rose to 103 F. A puncture was made and 75 c.c. of spinal fluid withdrawn. It was then decided to give 20 c.c. of antiserum. In ten hours his temperature was normal and he made an uninterrupted recovery.

Case 8.—*Patient.*—R. M., aged 17; electrician. Treated by Dr. W. S. Chase. Admitted May 25, 1907, at 1 p. m.

History.—Patient, who was an employé of a local rubber company, quit work at noon on May 24 because he did not feel well. He went home, but did not go to bed; refused supper, and later in the evening vomited. He went to bed early, complaining of headache, and was restless the greater part of the night. His headache was worse in the morning. He refused breakfast, and vomited again. About 10 a. m. he became unconscious.

Condition on Admission.—Temperature 105.2 F.; pulse 142; respiration 20; comatose—violent; pupils slightly contracted and reacted to light; no nystagmus; plantar reflex present, patellar slightly exaggerated, abdominal absent; Kernig sign present; no herpes; neck rigid and painful to move; sphincters intact. On puncture 15 c.c. opalescent fluid withdrawn; diplococci present; 15 c.c. serum injected.

May 26: Patient worse. Temperature 102.2 F.; pulse 100; respiration 6; cyanosed; puncture and withdrawal of 15 c.c. of fluid, stain of which showed diplococci. Died shortly after midnight.

CASE 9.—*Patient.*—G. G., aged 17; school girl. Treated by Drs. G. A. Theiss and A. F. Sippy. Admitted June 9, 1907, at 7 p. m.

History.—Patient was well until 24 hours before admission to the hospital, when she began to complain of malaise and headache. She vomited during the night and became unconscious at 2:30 p. m. June 9, just 4½ hours before admission to the hospital.

Condition on Admission.—Temperature 98.4 F.; pulse 108; respiration 20. Unconscious; comatose and very restless; pupils normal; no nystagmus; plantar, patellar and abdominal reflexes absent; Kernig sign positive; no herpes; neck

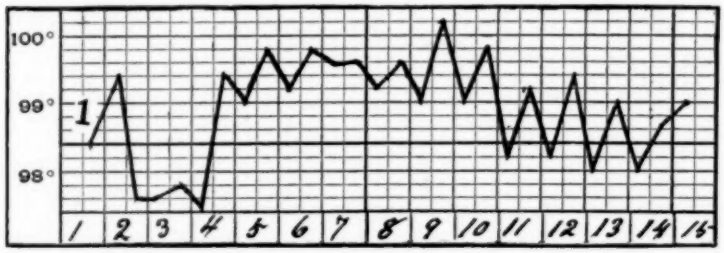


Fig. 6.—CASE 9.—(1) 90 c.c. cerebrospinal fluid withdrawn and 22.5 c.c. antiserum injected.

rigid; sphincters intact. Puncture yielded 90 c.c. of opalescent fluid; stain positive; 22.5 c.c. of antiserum injected.

June 10: Temperature at 6 a. m. 97.2 F.; pulse 102. Temperature subnormal all day; rational at times; slight opisthotonus and nystagmus. It was necessary to use a catheter.

June 11: Temperature subnormal all day; conscious and rational; abdominal and plantar reflexes present; patellar reflex absent; Kernig sign marked; neck rigid; herpes labialis; no pain.

June 12: Highest temperature 99.6 F.; pulse 84. Mental condition excellent; spoke of pain in head only when asked; reflexes all present; Kernig sign present; neck rigid and painful on movement; got out of bed and went to closet alone. Patient gradually improved from the fourth to the twelfth day of the disease. Reflexes all returned. Neck rigidity disappeared. Kernig sign disappeared. Appetite improved. Free from pain most of the time.

June 21: Temperature normal; sat up in chair; ate and slept well; no sequelæ.

June 23: Discharged, 15 days after admission.

The onset in this case was not very severe, although within 24 hours the patient was in a comatose condition and opisthotonus was marked.

All the reflexes were lost. Despite these symptoms and the presence of large numbers of the *Diplococcus intracellularis*, the patient's temperature was normal and the respirations were but slightly accelerated.

CASE 10.—*Patient.*—J. A. S., aged 24; postman. Treated by Dr. George Rankin. Admitted June 24, 1907, at 11 a. m.

History.—Patient had been well, and worked until the day before his admission to the hospital. On that day he attended a picnic and was exposed to the hot sun. He went home in the evening with headache and feeling ill. This he attributed to the effects of the sun. He did not sleep well and was restless, complained more of headache, and became unconscious about 5 a. m. July 24.

Condition on Admission.—Temperature 103.8 F.; pulse 70; respiration 36; comatose and very restless; face flushed; got out of bed; pupils moderately dilated, respond to light; plantar, patellar and abdominal reflexes absent; Kernig sign positive; no herpes; neck moderately rigid; involuntary urination and bowel movements; no nystagmus. Puncture yielded 90 c.c. of fluid; stain positive; 22.5 c.c. of serum injected.

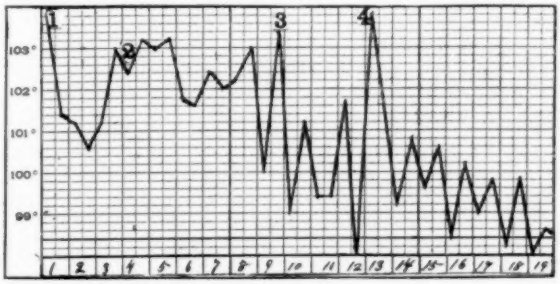


Fig. 7.—CASE 10.—(1) 90 c.c. cerebrospinal fluid withdrawn and 22.5 c.c. antiserum injected. (2) 45 c.c. cerebrospinal fluid withdrawn and 22.5 c.c. antiserum injected. (3) 60 c.c. cerebrospinal fluid withdrawn and 30 c.c. antiserum injected. (4) 45 c.c. cerebrospinal fluid withdrawn and 30 c.c. antiserum injected.

June 25: Temperature at 6 a. m. 101.2 F.; pulse 60. At 12 m. temperature 100.6 F.; pulse 64. Semiconscious; responds when spoken to, but mutters unintelligibly when attempting to form sentences; restless at times; knee reflex absent; plantar and abdominal reflexes present; neck more rigid; Kernig sign present; pupils equal, dilated and respond to light.

June 26: Temperature at 6 a. m. 101.2 F.; pulse 64. At 12 m. temperature 103 F.; pulse 72. Conscious and rational; neck less rigid; some headache.

June 27: Temperature at 6 a. m. 102.4 F.; pulse 70. At 12 m. temperature 103.2 F.; pulse 92. Herpes labialis appearing. At 2 a. m. puncture gave 45 c.c. of fluid; 22.5 c.c. of serum administered. At 9 a. m. rational; singing and talking with other patients; reflexes improved; Kernig sign present; neck rigid; involuntary urination.

June 28: Temperature at 6 a. m. 103 F.; pulse 74. At 12 m. temperature 102 F.; pulse 80. Mental condition good; some pain in back of neck.

June 29: Temperature at 6 a. m. 101.8 F.; pulse 80. At 12 m. temperature 101.2 F.; pulse 74. Same condition as on preceding day. Pain in back of neck and head.

June 30: Temperature at 6 a. m. 102.4 F.; pulse 72. At 12 m. temperature 101.6 F.; pulse 80. Condition good; reflexes all present; Kernig sign present; neck rigid and painful on movement; some headache; herpes labialis extensive and painful.

July 2: Temperature at 6 a. m. 100.4 F.; pulse 70. At 9 p. m. temperature 103.6 F.; pulse 80. Condition the same as on preceding day. At 9 p. m. puncture gave 60 c.c. of fluid; 30 c.c. of serum injected.

July 3: Temperature at 6 a. m. 99 F.; pulse 70. At 12 m. temperature 100 F.; pulse 74. Condition improved; feels better.

July 4 to 6: No essential change, except for pain in testicles; not red or swollen, but very painful to touch.

July 6: Puncture yielded 45 c.c. of slightly cloudy fluid; 30 c.c. of serum injected; stain positive.

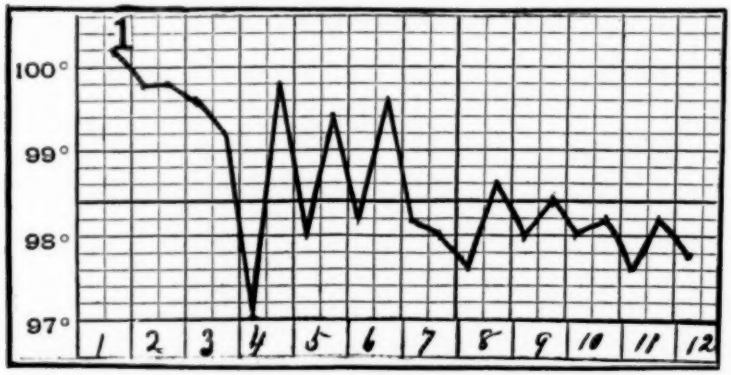


Fig. 8.—CASE 11.—(1) 75 c.c. of cerebrospinal fluid withdrawn and 25 c.c. antiserum injected.

July 7: Temperature at 6 a. m. 99.2 F.; pulse 72. At 12 m. temperature 99.8 F.; pulse 84. Patient feels well; no pain.

July 8: Temperature at 6 a. m. 99.6 F.; pulse 80. At 12 m. temperature 99.2 F.; pulse 70. No pain; appetite excellent.

July 9: Temperature normal; no pain; no neck rigidity. Temperature remained normal from this day on.

July 14: Sat up in bed. Patient continued to improve, grew stronger, walked about the ward, and was discharged July 24 at 3 p. m., 31 days after admission to the hospital. Reported since that he can not stand the hot sun; it causes him intense headache.

CASE 11.—*Patient.*—E. R., aged 20; machinist. Treated by Drs. C. T. Hill and J. H. Seiler. Admitted June 30, 1907, at 9:50 p. m.

History.—Patient worked all day Saturday preceding, and went to church Sunday morning feeling well. He came home and did not eat much dinner, having a little headache. After dinner he lay down in the yard in the shade for a

while; then went upstairs to bed. He was found about 3 p. m. lying on the floor in an unconscious state, rolling about at times and throwing his hands to his head.

Condition on Admission.—Temperature 100.2 F.; pulse 80; respiration 18; unconscious; comatose; restless, moaning and throwing his hands to his head; pupils normal; no nystagmus; plantar and patellar reflexes exaggerated, abdominal absent; Kernig sign present; no herpes; neck slightly rigid and painful on movement; sphincters intact. Puncture yielded 75 c.c. of opalescent fluid; stain showed diplococci; 25 c.c. of serum injected.

July 1: Temperature at 6 a. m. 99.8 F.; pulse 80; slight convulsion, lasting 20 minutes, at 3 a. m.; vomited several times during the day. Temperature at 12 m. 100 F.; pulse 60; restless and moaning.

July 2: Temperature at 6 a. m. 99.6 F.; pulse 54. Much improved; rational; reflexes all present; Kernig sign less marked; neck still rigid, but not so painful on movement; some pain in head; mentality good. Temperature at 6 p. m. 99.2 F.; pulse 68.

July 3: Temperature at 6 a. m. 97; pulse 62. Condition excellent; only complaint is pain over eyes. Temperature normal most of the day; at 6 p. m. 99.8 F.; pulse 72.

July 4: On this the fourth day of the disease temperature was normal and remained so. Reflexes all present and normal.

July 9: Patient sat up in a chair.

July 11: On this day, 12 days after admission, patient was discharged, walking to the street car.

The onset here was abrupt and severe. This case was received at the hospital earlier than any of the others. From the appearance of premonitory symptoms to the time of the first injection only 12 hours had elapsed. He then received 25 c.c. of serum. Following this early large dose, his symptoms rapidly abated.

CASE 12.—*Patient.*—H. B., aged 6; schoolgirl. Treated by Dr. Charles E Norris. Admitted Sept. 11, 1907, at 1:30 p. m.

History.—Patient attended school Monday, Tuesday and Wednesday, but stayed at home Thursday with a sprained ankle. Friday she suffered with a severe headache; had paroxysms of pain, and put her hands to her head and cried out. She then passed into a semi-comatose state. This continued until Tuesday morning about 11 o'clock, when she went into a comatose state and so remained until the time of her admission to the hospital. On admission her head was not drawn back, but neck was rigid and on attempting to move it her facial expression was that of a person in pain. The same was true in eliciting Kernig's sign. Abdomen was retracted; *tâche cérébrale* present; tongue and mouth dry, and sordes on tongue and teeth. Patient had been treated from Friday until Tuesday for intestinal trouble, and on Wednesday the death sentence was pronounced.

Condition on Admission.—Temperature 102.6 F.; midnight, 103.4 F. Pulse 132; midnight, 138. Respiration 22; midnight, 28. Unconscious; comatose; pupils moderately dilated, but reacted to light; plantar, patellar and abdominal reflexes absent; Kernig sign present; no herpes; neck rigid; sphincter control lost; nystagmus at times. On puncture 35 c.c. of clear fluid was withdrawn, and 30 c.c. of serum injected; stain positive. It was feared that the child would die while the puncture and injection were being made. No anesthetic.

September 12: Temperature at 6 a. m. 103.4 F.; pulse 124. Temperature at 12 m. 101.4 F.; pulse 114. Semi-conscious; respiration more regular; complete

paralysis of legs and right arm, but moved left arm at times. Puncture at 1 p. m. gave 35 c.c. of fluid; 30 c.c. of serum injected; stain positive. Involuntary urination and bowel movements; reflexes absent; neck rigid.

September 13: Temperature at 6 a. m. 101 F.; pulse 110. Temperature at 9 p. m. 100.4 F.; pulse 94. Improved; responds when spoken to; takes nourishment; reflexes all absent. Puncture at 10 p. m. gave 30 c.c. of fluid; 30 c.c. of serum injected. Neck rigid.

September 15: Temperature 99.8 to 100.4 F.; pulse 96. Improved; mental condition better; pronates and supinates left arm; complains of pain on being moved.

September 17: Condition about the same. Neck not so rigid; moves it laterally. Pain on pressure over muscles and large nerve trunks; reflexes absent.

September 19: Somewhat better; enjoys being played with; moves both arms somewhat, also toes; plantar reflex present for first time, others absent; nerves respond to Faradic current; tactile, thermal, and pain senses all present.

September 21: General condition better; plays with doll and laughs. Puncture at 9:30 p. m. gave 40 c.c. of fluid; 30 c.c. of serum injected.

September 22: Temperature at 6 a. m. 101 F.; pulse 108. Temperature at 12 m. 99.2 F.; pulse 112. Condition about the same as on preceding day; somewhat irritable; no rigidity of neck; muscular soreness.

September 23: Moves hands better; abdominal reflex on right side; irritable; small ulcer above inion; plantar reflex present at all times; others absent; no neck rigidity.

September 24: Urticaria over extensor surfaces.

September 26: No change, except for adenopathy on right side of neck.

September 28: Temperature at 6 a. m. 100.4 F.; pulse 116. Temperature at 6 p. m. 102 F.; pulse 136. Adenopathy more marked; moves arms and toes freely and left knee slightly.

September 29: Adenopathy on both sides; sphincter control improved; reflexes the same.

October 4: Urticaria gone; adenopathy more marked. Puncture at 9 p. m. gave 75 c.c. of fluid; 25 c.c. of serum injected. Right side of neck incised and drained; reflexes the same.

October 5: Temperature at 6 a. m., 102.8; pulse, 134. Temperature at 9 p. m., 102.4 F.; pulse, 140. Condition about the same as on preceding day; pain in neck.

October 7: Temperature at 6 a. m., 100.6 F.; pulse, 110. Temperature at 9 p. m., 100.6 F.; pulse, 108. Condition improved; adenopathy improved; no more involuntary urination or bowel movements.

October 11: Condition same as on preceding three days. Puncture at 9 p. m. yielded 65 c.c. of fluid; 15 c.c. of serum injected.

October 12: Internal squint of right eye; pain on being moved; adenopathy disappeared.

October 13: Squint in both eyes; pupils equal and react; erythema on back.

October 15 to 23: Temperature but slightly above normal; moved arms and fingers a little better each day.

October 23: From this day on the child had normal temperature and pulse, was not so irritable, and ceased to have pain on being moved. Her mental condition was good—her people say as good as it ever was. The paralysis improved considerably before she was discharged, so that she was able to feed herself; could invert and evert both feet; moved the left knee very well, and also the toes. She enjoyed sitting up in a wheel chair. She gained about 15 pounds in weight while at the hospital, and her appetite and digestion were good all the time. Reflexes did not improve. On the date of her discharge, plantar reflex was

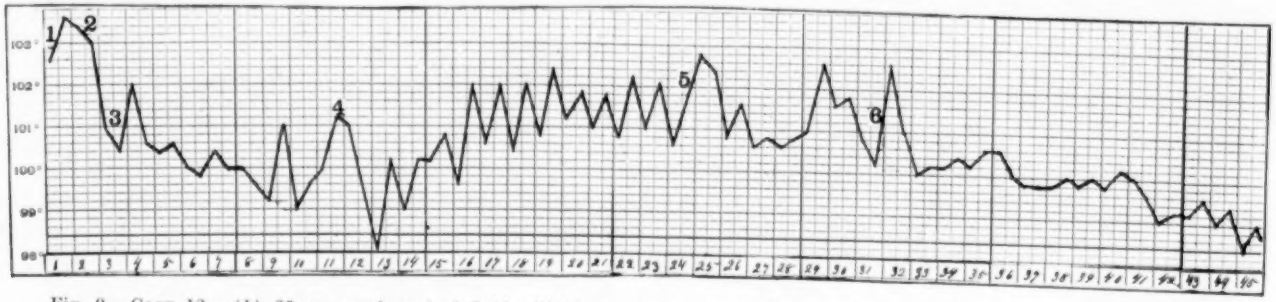


Fig. 9.—Case 12.—(1) 35 c.c. cerebrospinal fluid withdrawn and 30 c.c. of antiserum injected. (2) 30 c.c. cerebrospinal fluid withdrawn and 30 c.c. antiserum injected. (3) 30 c.c. cerebrospinal fluid withdrawn and 30 c.c. antiserum injected. (4) 40 c.c. cerebrospinal fluid withdrawn and 30 c.c. antiserum injected. (5) 75 c.c. cerebrospinal fluid withdrawn and 25 c.c. antiserum injected. (6) 65 c.c. cerebrospinal fluid withdrawn and 15 c.c. antiserum injected.

present, patellar absent, abdominal present on right side only; Kernig sign absent. She still had some internal squint of both eyes, but it had improved; pupils equal and reacted to light and accommodation. She knew her letters and could see to read them and also to count. She was discharged Nov. 13, 1907, the sixty-fourth day after entering the hospital.

This case ran a very severe and protracted course. The first puncture was made without an anesthetic of any kind, and 30 c.c. of serum were injected. As stated, the child collapsed under this procedure, and it was thought for a time that she would not revive. On the second and third days thereafter punctures were made and antiserum injected. She was semi-conscious on the second day, rational and able to take nourishment on the third day. It will be noted that a small decubitus ulcer developed over the inion on the thirteenth day, and it was undoubtedly from this source that there resulted an infection of the cervical lymph glands noted in the history. Part of the fever and irritability from the sixteenth to the twenty-sixth day might certainly be attributed to this infection.

Cases.	Day of Disease, First Injection.	Total Number Injections.	Total c.c of Anti-serum Injected.	Total c.c. Spinal Fluid withdrawn.	Complication.	Sequelæ.	Results.
1	7	6	82.5	330	None. . . .	Kyphosis. .	Recovery by lysis.
2	2	1	10.0	120	. . . . .	. . . . .	Death
3	15	1	20.0	60	Nephritis. .	None. . . .	Recovery by crisis.
4	10	1	25.0	90	Nephritis neuritis, furuncles.	None. . . .	Recovery by crisis.
5	2	4	43.5	169	Neuritis. . .	None. . . .	Recovery by lysis.
6	2	2	22.5	105	. . . . .	. . . . .	Death.
7	1	2	35.0	150	None. . . .	None. . .	Recovery by crisis.
8	2	1	15.0	30	. . . . .	. . . . .	Death.
9	1	1	22.5	90	None. . . .	None. . . .	Recovery by crisis.
10	2	4	105.0	240	None. . . .	Headache in sun.	Recovery by lysis.
11	1	1	25.0	75	None. . . .	None.	Recovery by crisis.
12	6	6	160.0	275	Adenitis, strabismus, paralysis of extremities.	Partial paralysis of extremities.	Recovery by lysis.

CONCLUSIONS.

Although the figures given above record 75 per cent. of recoveries in cases treated with the antiserum, we feel that it is really unfair to put Case 2 in the failure column, for the serum was not used until some time after the patient had become pulseless. In Case 6 the improvement following the first injection was as marked and as satisfactory as in any of those which went on to recovery. Death came suddenly and without a warning. The remaining case which resulted fatally was of the most pronounced fulminating type.

While we have not the clinical records of the cases outside the hospital which did not receive the antiserum, all of which died but one, we certainly have the right to assume that, occurring in the same epidemic, the difference in mortality in these cases as compared with those that received the antiserum was not due simply to their having been of much greater average severity.

THE PRESENCE OF ANTAGONISTIC SUBSTANCES IN THE BLOOD SERUM IN EARLY AND LATE SYPHILIS AND IN PARESIS AND TABES.*

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The appearance of the work of Wassermann, Neisser and Bruck,[1] and of Wassermann, Neisser, Bruck and Schucht[2] describing a positive serum reaction in syphilis by means of Wassermann's modifications of the Bordet-Gengou method of complement binding, gave an impetus to the study of serum reactions in syphilis, paresis and tabes, and of the diagnostic value of the results obtained. The reaction of Wassermann, Neisser and Bruck is based in principle on the specific binding of complement, such as occurs, for instance, in the presence of an immune precipitin containing serum and the corresponding precipitinogen. In the reaction the antigen is represented by an extract of the liver of a syphilitic fetus, and the antibody is contained in the blood serum of a syphilitic patient or in either the blood serum or cerebrospinal fluid, or both, of a paretic or tabetic patient.

To carry out a test for the reaction one mixes in test tubes definite quantities of the liver extract and the inactivated blood serum (or cerebrospinal fluid) and adds complement. After standing one hour in the incubator to allow for the binding of the complement, an inactive immune hemolytic serum, with its corresponding corpuscles, is added and the tubes are returned to the incubator, where they remain for two hours. At the end of this length of time they are taken out and examined for evidences of hemolysis. A final opinion, however, as to the presence and degree or absence of hemolysis is best deferred until after the tubes shall have remained over night in the ice chest. In the case of a positive reaction, the evidence that complement has been bound and thus diverted from the hemolytic amboceptor of the immune serum is afforded by the fact that hemolysis has not occurred.

As in other hemolytic experiments, perhaps even to a greater extent than in those, it is essential that a number of control tests be made. For example, in addition to the customary system controls, the extract and serum should be tested separately for both hemolytic and anti-hemolytic

* From the Rockefeller Institute for Medical Research, New York.

1. Deutsche med. Wchnschr., 1906, xxxii, 745.
2. Ztschr. f. Hyg. u. Infektionskrankh., 1906, lv, 451.

effect, and together, without the addition of complement, for hemolytic effect. Furthermore, it should be shown that the liver extract with normal or non-syphilitic serum does not bind complement, etc.

As regards the nature of the substances on whose interaction the binding of complement depends, there exist certain differences of opinion. Without discussing the question at length, it may be said that Wassermann believed in the beginning that the substances were directly related in origin to *Spirochæta pallida*. Later he held that the reaction is only a serum diagnosis of some substance which was formerly unknown to us, and which stands in some relation to the syphilitic infection. Citron,[3] on the other hand, while fully confirming the specificity and diagnostic value of the reaction, believes that the nature of the substances can not be determined definitely until the spirochete has been grown in pure culture. Nevertheless, he suggests that during the course and in consequence of the syphilitic infection certain products of cell metabolism may lead to auto-immunization, and that it may be to these substances, with their corresponding antibodies, that the reaction is due. According to Levaditi and Yamanouchi,[4] the antigen may be represented by sodium taurocholate and glycocholate, and to a less extent by lecithin. Finally, Weil and Braun[5] believe that some substance besides lipoids may be responsible for the reaction, inasmuch as they obtained it with extracts of liver, from which the lipoids had been removed by repeated shaking with petroleum ether.

Notwithstanding the doubt which surrounds the cause and nature of the Wassermann reaction in syphilis, its value as a diagnostic means would seem to have been confirmed by the observations of Detre,[6] Citron,[7] Marie and Levaditi,[8] Meier,[9] Michaelis and Lesser,[10] and many others. In considerably more than 1,000 cases of syphilis in all stages, in paresis and in tabes a positive reaction has been obtained in approximately 80 per cent. of the number. While with normal and non-syphilitic serum the occurrence of the reaction has been reported only once, namely, in frambesia tropica, by Blumenthal.[11] This last result is less surprising when we consider the similarity which yaws bears to syphilis.

3. Berl. klin. Wchnschr., 1907, xliv, 1370.
4. Compt. rend. Soc. de Biol., 1907, lxiii, 740.
5. Wien. klin. Wchnschr., 1908, xxi, 151.
6. Wien. klin. Wchnschr., 1906, xix, 619.
7. Deutsche med. Wchnschr., 1907, xxxiii, 1165.
8. Ann. de l'Inst. Pasteur, 1907, xxi, 138.
9. Berl. klin. Wchnschr., 1907, xliv, 1636.
10. Berl. klin. Wchnschr., 1908, xlv, 301.
11. Deutsche med. Wchnschr., 1908, xxiv, 258.

As has been pointed out, this reaction is concerned mainly, at least from a clinical standpoint, with the demonstration of an antibody. To be sure Wassermann, Neisser, and Bruck[1] drew attention to the fact that the ability to demonstrate antigen in the body fluids of syphilitics would be of considerable importance in diagnosis and treatment. They even succeeded in doing so in a few instances in which they used as an antibody-containing fluid the serum of apes immunized with syphilitic material. Usually, however, the attempt has failed; possibly, they suggest, on account of the difficulty of obtaining a sufficiently strong immune serum.

Recently Fornet, Schereschewsky, Eisenzimmer and Rosenfeld,[12] by means of a direct method, as opposed to the above, which may be considered as an indirect one, claim to be able to show the presence of either syphilitic antigen or antibody in the blood serum. The method is essentially that advocated by Ascoli in carrying out the usual precipitin test. On bringing into contact the serum from a patient with early syphilis and that from a paretic or tabetic, Fornet observed a delicate ring of cloudiness at the zone of contact. The ring never occurred when either pathologic serum in the test was replaced by a normal serum. The cloud is due, according to Fornet, to the precipitate which results from the interaction of "lues-precipitinogen," arising directly from the spirochetæ themselves, and its corresponding "lues-precipitin." Inasmuch as the production of precipitin demands the preceding occurrence within the organism of precipitinogen, Fornet concludes that it is precipitinogen which is present in early syphilis and precipitin in later conditions as in paresis and tabes. In a few instances he found precipitinogen in paresis and tabes, i. e., the serum from one paretic or tabetic gave a ring with the serum from another. This apparent discrepancy is explained by the assumption that in the instances where precipitinogen was present the syphilitic process was still active within the body.

Assuming the correctness of the observations and deductions of Fornet and his associates, it would appear that complement would be bound if added to a mixture of serum derived from a patient with early syphilis (presumably containing precipitinogen) and serum derived from a paretic or tabetic (presumably containing precipitin), since it is always bound in the presence of a specific precipitin reaction. Indeed, in view of the extreme delicacy of the binding reaction (Neisser and Sach's modification of the forensic precipitin test), it might be expected to reveal the presence of quantities of precipitinogen in syphilis too minute to produce

12. München med. Wchnschr., 1907, liv, 1471; Deutsche med. Wchnschr., 1907, xxxiii, 1679.

a visible precipitate. Consequently, in our attempts to show the presence of antagonistic substances in the two varieties of sera, we have used both the methods of complement deviation and precipitation.

Material was placed at our disposal through the kindness of Dr. Moore of the Manhattan State Hospital and of Drs. Mitchell and Eckert of the City Hospital. The sera of nineteen individuals were tested in various combinations. From patients with secondary syphilis with active manifestations there were seven specimens; from tertiary syphilis (gumma), one specimen; from paresis, four specimens; tabes, one specimen, and from normal persons, six specimens. In the binding experiments, the technic of Wassermann and his pupils was followed, except that the liver extract was replaced by serum from a patient with secondary syphilis. The results of these tests were uniformly negative, as is shown in Table 1:

TABLE 1.

						Result.
Serum	M., secondary syphilis	+	Serum	W. A., paresis		Negative
Serum	J., secondary syphilis	+	Serum	W. A., paresis		Negative
Serum	V., secondary syphilis	+	Serum	M., tertiary syphilis		Negative
Serum	J. S., secondary syphilis	+	Serum	R., tabes		Negative
Serum	J. S., secondary syphilis	+	Serum	R. B., paresis		Negative
Serum	J. S., secondary syphilis	+	Serum	T. C., paresis		Negative
Serum	J. T., secondary syphilis	+	Serum	W. P., paresis		Negative
Serum	M., secondary syphilis	+	Serum	J., normal		Negative
Serum	W. A., paresis	+	Serum	J., normal		Negative
Serum	V., secondary syphilis	+	Serum	M., normal		Negative
Serum	M., tertiary syphilis	+	Serum	M., normal		Negative
Serum	J. S., secondary syphilis	+	Serum	C., normal		Negative
Serum	R., tabes	+	Serum	C., normal		Negative
Serum	J. S., secondary syphilis	+	Serum	G., normal		Negative
Serum	R. B., paresis	+	Serum	G., normal		Negative
Serum	T. C., paresis	+	Serum	G., normal		Negative

The sera were employed in quantities of 0.2 c.c. and 0.1 c.c. In each experiment, the following control tests were made:

TABLE 2.

Serum 1.	Serum 2.	Complement guinea pig.	Immune rabbit serum, anti-sheep.	Sheep's corpuscles, 5 per cent.	Result in terms of hemolysis.
0.3	...	...	.....	1	—
...	0.3	...	.....	1	—
0.2	0.1	...	0.002	1	—
0.3	...	0.1	0.002	1	+
...	0.3	0.1	0.002	1	+
...	...	0.1	0.002	1	+
...	...	0.1	.....	1	—
...	...	...	.....	1	—
...	...	...	0.002	1	—

The results with the precipitate reaction in contrast to the above were not uniform, but quite variable and indecisive. Nine tests were made with serum from patients with secondary syphilis (supposed to

contain precipitinogen) and serum from patients with tertiary syphilis, paresis and tabes. Of these, three were positive and six negative. Normal serum was tested with the serum from patients with secondary syphilis six times, with three positive and three negative results; with one serum from tertiary syphilis, with positive result; with one serum from tabes with negative result, and with three sera from paresis, with one positive and two negative results. Twice the serum from one patient with secondary syphilis was tested against the serum from another patient in the same stage of syphilis, with one positive and one negative result. And, finally, one normal serum was tested in the undiluted state with its own dilutions of one to five and one to ten. Table 3 shows the inconstancy of the results.

TABLE 3.

Serum S. secondary syphilis.			Serum T C. paresis.			Serum R. B. paresis.			Serum G. normal.			Result. After.	
Native.	1 to 5.	1 to 10.	Native.	1 to 5.	1 to 10.	Native.	1 to 5.	1 to 10.	Native.	1 to 5.	1 to 10.	2 hours.	16 to 20 hours.
×	..	..	×	..	..	..	..	..	..	..	..	—	—
×	..	..	..	..	..	×	..	..	..	..	..	—	—
×	..	..	..	..	..	..	..	..	×	..	..	—	—
..	×	..	×	..	..	..	..	..	..	..	..	+	+
..	×	..	..	..	..	×	..	..	..	..	..	+	—
..	×	..	..	..	..	..	..	..	×	..	..	—	—
×	..	..	..	×	..	..	..	..	..	..	..	—	—
×	..	..	..	..	..	..	×	..	..	..	..	—	—
×	..	..	..	..	..	..	..	..	..	×	..	+	—
×	..	..	..	..	×	..	..	..	..	..	..	—	—
×	..	..	..	..	..	..	..	×	..	..	..	—	—
×	..	..	..	..	..	..	..	..	..	..	×	+	—
..	..	..	×	..	..	..	..	..	..	..	×	—	—
..	..	..	..	..	..	×	..	..	..	..	×	+	+
..	..	..	×	..	..	..	..	..	×	..	..	—	—
..	..	..	..	..	..	×	..	..	×	..	..	—	—
..	..	..	×	..	..	..	..	..	..	×	..	—	—
..	..	..	..	..	..	..	..	..	×	×	..	+	—
..	..	..	..	..	..	..	..	..	×	..	×	+	+

In employing the test, it is absolutely necessary that the sera be perfectly clear. On account of the delicacy and fineness of the rings, a certain amount of practice is required for a correct reading of results. Sometimes in our experiments the rings appeared within two hours, sometimes not until the following morning, and sometimes those which appeared within two hours persisted until the following morning and sometimes not. With two exceptions the cloud appeared only when one or the other serum was employed in the diluted state. A temperature of 37 C. seemed to have no effect on the reaction. While not attempting to explain the occurrence of the rings, whether they are merely optical phenomena or

real precipitates of some undetermined substance, we feel unjustified in believing that they are necessarily the result of a specific reaction between lues-precipitinogen and lues-precipitin.

Recently Plaut, Heuck, and Rossi[13] have reported results with the precipitate reaction which are quite similar to those described above. With the combination of serum from syphilitic patients and serum from paretics they reported six positive and ten negative results; with serum from syphilitic patients and normal serum, four positive and four negative results; with normal serum and serum from paretics, six positive, five negative. Two experiments, in which the serum of one patient with secondary syphilis was tested with the serum from another patient with secondary syphilis, gave negative results. Of two tests with serum from one normal person and serum from another normal person, one was positive and one negative. Finally, when one normal serum was tested with its own dilutions there were three positive results and one negative result.

They believe that the ring of a positive reaction is an actual precipitate, but of what nature they are not prepared to say. The difference in the density of the two media appeared to have an influence upon the occurrence of the reaction, since in their tests a positive result was never obtained when both sera were used undiluted. Although considering it possible that by means of precipitation a specific reaction for syphilis may be found, they conclude that in its present form the precipitate reaction has no place in diagnosis.

CONCLUSION.

Neither by the complement-binding method nor by the method of precipitation as at present carried out is it possible to show the presence of antagonistic substances in the blood serum of patients in the secondary stages of syphilis on the one hand and in the tertiary stage on the other, or in such parasyphilitic affections as paresis and tabes.

Rockefeller Institute for Medical Research.

13. Münch. med. Wchnschr., 1908, lv, 66.

CLINICAL MANIFESTATIONS OF HEMORRHAGIC RENAL INFARCT.

REVIEW OF LITERATURE. REPORT OF A CASE.

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While a most thorough knowledge regarding the pathology of renal infarct exists to-day, as a result of the classical studies of Virchow, Rokitansky, Cohnheim, Litten, Ribbert and others, very little has been said or written about its clinical manifestations. This undoubtedly must be attributed to the fact that renal infarct, as a clinical entity, is extremely rare, and that, while small infarcts are not infrequently found postmortem, they are very rarely manifested clinically.

To quote Senator: "Symptoms referable to hemorrhagic infarction of the kidney are rarely observed unless the infarcts are unusually large or numerous, when there may be well marked symptoms, of which sudden pain in the corresponding kidney, aggravated by pressure, and the appearance of blood and hemoglobin in the urine, are somewhat characteristic."

Leube makes the following statement: "Cases where hemorrhagic kidney infarcts were diagnosed antemortem are very rare. I was able to diagnose the condition in only one case."

The experience with my own case and careful study of cases from the literature convinced me that renal infarcts, while rarely sufficiently large, are capable, at times, of producing a sharply cut clinical picture of their own, and are, therefore, worthy of special study.

A few words regarding the causation of renal infarcts may not be amiss here.

Renal infarction can be produced by occlusion of the renal artery itself or of one or several of its branches. Occlusion of the renal artery may be the result of an autochthonous thrombosis from local causes or it may be due to embolism. By far the most common cause is arterial embolism. The causes are the same as those of embolism elsewhere—the lodgment of clots, of inflammatory deposits from the left side of the heart or from the aorta, particles of tumors, micro- and macroparasites, particles of pigment and of calcium that have gotten into the arterial circulation. Diseases of the left side of the heart are the predominating etiologic factors, as will be seen from the review of cases. Arterial thrombosis is extremely rare in the renal arteries, and, as in the case of

other arteries, it is the result of diseases of the vessel wall, particularly endarteritis, arteriosclerosis, amyloid degeneration, and injury to the coats.

REVIEW OF LITERATURE.

Traube, in 1856, was the first to diagnose and report a case of renal infarct. Leube mentions one case, which he diagnosed, in his "Specielle Diagnose der inneren Krankheiten" (1891, p. 325).

Four more cases reported by various authors were diagnosed postmortem. Rudolph Schmidt was really the first clinician who made a thorough study of this condition. He reported three cases from Neusser's clinic, all of which he diagnosed antemortem. An idea of the meagerness of literature on the subject can be gathered from the fact that I was able to collect only ten cases, besides my own.

With regard to etiology these cases group themselves as follows: (1) Those due to arterial embolism, the result of a valvular lesion of the heart; (2) those due to arterial embolism, the result of an infectious process other than endocarditis; (3) those due to local arterial disease, with thrombus formation. The last group is represented by only two cases—one case reported by von Recklinghausen, in which the thrombus formation was due to injury of the renal artery, and by my own case, in which the thrombus formation was the result of an obliterating endarteritis of the renal arteries and their branches. The second group includes two cases, while the first comprises the remaining seven.

CASE 1.—(Traube[1]). *History.*—This celebrated case occurred in a machinist, 18 years old, who suffered from aortic insufficiency combined with dilatation and hypertrophy of both ventricles. On October 14 the patient was awakened from sleep at 1 a. m. by a very intense pain in the region of the right kidney. The pain radiated into the right thigh. There was some suppression of urine, but no albumin or blood. The pain subsided considerably. On October 19 there was sudden onset of vomiting, with general collapse. Death occurred four days later, preceded by marked anxiety, restlessness and air hunger.

Autopsy.—Warty vegetations on the semilunar valves. Spleen contained one infarct size of a hazelnut. Both kidneys contained numerous small infarcts. The right kidney contained one large infarct which protruded slightly above the cut surface. The infarct measured two inches at its base and extended to the hilus.

CASE 2.—(Bartels[2]). *History.*—Boy, 8 years old, tracheotomized for croup, suddenly developed pain in the region of the spleen, followed by enlargement of the organ. Several days later he developed pain in the left thigh, followed shortly by paralysis of the extremity. There were no urinary symptoms. Patient died four days after onset.

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1. Ueber den Zusammenhang von Herz und Nierenkrankheiten, Berlin, 1856, p. 77.

2. Cited from "Untersuchungen über die Embolishe Processe, von Dr. Jul. Cohnheim," 1872.

Postmortem.—A large infarct of the spleen. Right kidney normal. Left kidney contained a large infarct. Left renal artery and its branches were thrombosed. There was no endocarditis.

CASE 3.—(Yuhel Renoy[3]). *History.*—Girl, 16 years old, convalescing from scarlatina. Developed pain in both lumbar regions on the second day of normal temperature. Pain was not very intense. She was catheterized daily without result. Patient died after six days of total anuria, but without uremic symptoms.

Autopsy revealed no cardiac or aortic lesion. Both kidneys were entirely necrosed. Multiple emboli were found in the renal arteries and in the glomerular tufts.

CASE 4.—(von Jurgensen[4]). *History.*—A woman, 27 years old, suffering from a double mitral lesion. This patient had three attacks of pain from November 8 to January 29. Pain was on the right side, ushered in suddenly and accompanied by marked albuminuria, but no blood. Each attack lasted from three to four days.

Autopsy.—Endocarditis, new vegetations engrafted on an old valvular lesion. Infarction of spleen. Left kidney was normal in size and contained small cortical infarcts. Right kidney was about one-fourth the normal size, and almost entirely necrotic. The right renal artery was completely blocked by red thrombi.

CASE 5.—(von Leube[5]). *History.*—Cabinet maker, 17 years old. Suffered from recurrent attacks of rheumatic arthritis. Showed aortic insufficiency. This patient had two attacks of pain in both kidney regions. Urine, previous to each attack, was normal. With each attack there appeared blood and albumin. Case was diagnosed as one of renal infarction. Patient recovered.

CASE 6.—(R. Schmidt[6]). *History.*—Laborer, 40 years old, suffering from recurrent attacks of rheumatic arthritis, associated with mitral insufficiency, suddenly developed a very intense pain in the right lumbar region. Pain did not radiate to genitalia or thigh, and was increased on palpation. There were no urinary changes. Diagnosis of infarct of the right kidney was made.

Autopsy showed a double mitral lesion, fresh anemic infarcts of the right kidney with hemorrhages into the capsule.

CASE 7.—(R. Schmidt[6]). *History.*—A girl, 21 years old, who had had four attacks of acute rheumatic arthritis, and who also had symptoms of mitral stenosis, developed a sudden pain, first in the left lumbar region, later in both right and left. In the previously normal urine there were found red cells and albumin, the latter in abundance. There was also a marked oliguria, the patient passing about 200 c.c. in twenty-four hours. Was diagnosed as bilateral kidney infarction.

Autopsy.—Endocarditis, double mitral lesion. Splenic infarcts. Numerous infarcts in both kidneys, largest 4½ by 1 cm.

CASE 8.—(R. Schmidt[7]). *History.*—Male, 45 years old, suffering from a double mitral lesion, developed a sudden severe pain, first in the right, later in both right and left kidney regions. There was suppression of urine with albumin, casts, and few red cells. Pain subsided four days later. Two days after subsidence of pain the patient developed a right sided hemiplegia and died from symptoms of cerebral apoplexy.

Antemortem *diagnosis* was, bilateral kidney infarction, embolism of the left Sylvian artery.

Postmorten findings established the correctness of the clinical diagnosis.

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3. Traite de Medicine, v, 643.
4. Nothnagel's Handb., xv, 105.
5. Specielle Diagnose der inneren Krankheiten, 1891, p. 325.
6. Wien. klin. Wchnschr., 1901, p. 451.
7. Wien. klin. Wchnschr., 1902, p. 643.

CASE 9.—(Georg Riebold[8]). *History.*—Servant girl, 29 years old, suffering from broken compensation due to double mitral lesion, the result of an old articular rheumatism. Two months after admission to hospital was suddenly seized with a very intense pain in the left side. Pain was well localized and did not radiate. It subsided slowly in the course of two days. There was retention of urine and some suppression, but no albumin, blood, or casts. There was slight fever and a leucocytosis of 21,600. On the third day, the patient developed pain in the corresponding region on the opposite side. On the fifth day she developed paresis of the right arm and leg and of the lower branches of the right facial nerve. Died on the sixth day of respiratory paralysis.

Postmortem Findings.—Mitral stenosis and insufficiency. Embolism of the basilar artery. Upper half of the left kidney infarcted, lower containing several small infarcts. Injection of the perirenal tissue. Embolus of the left renal artery extending into its upper branch and occluding it. Several small infarcts of the right kidney. Spleen contained an infarct, size of a cherry.

CASE 10.—(von Recklinghausen[10]). *History.*—In this case was found postmortem, in a boy who died eight days after sustaining severe internal injuries—the result of a fall—a circular injury to the coat of the left renal artery. This was about two lines in length and one in width; ½ cm. below this was a large red thrombus. All of the branches of the artery were likewise thrombosed. The kidney was entirely necrosed. This case established two important points: (1) That kidney infarcts may be produced by trauma to renal vessels; (2) that formation of typical necrotic infarcts is accomplished in a relatively short time.

CASE 11.—(Author's Case). *History.*—Man, 44 years old, married. Entered Michael Reese Hospital, Nov. 29, 1905, giving the following history: One year ago, after a drive on a cold day, he experienced painful, cramp-like sensation in the big toe of the left foot. Since then had occasional cramp-like sensations in the toe. Five weeks ago pain became very severe. Examination showed lividity of the lower third of the leg and of the foot. Heart was normal, urine negative. Gangrene of the big toe and later of the other toes and of the foot followed within a short period of time. Patient suffered most agonizing pain and was kept almost continually under the influence of morphin. Gangrene steadily progressed upward. The condition was then diagnosed as Raynaud's disease. Three weeks after admission patient developed high temperature, rigors, sweats and cough.

Examination.—Several foci of dulness and harsh breathing were found in the lungs. An ascending thrombophlebitis, proceeding from the gangrenous area upward, was detected. Urine now showed albumin and casts, but no blood. The presumption was that the patient had infected himself by scratching the painful foot. The extremity was amputated, and the patient recovered in about two weeks. He re-entered the hospital July 2, 1907, after a lapse of eighteen months, complaining of a continuous pain in the left upper quadrant of the abdomen of two weeks' duration, vomiting every morning, and cramp-like pain in the calf. During this second stay in the hospital the man had two attacks of pain, each lasting about four days. They were characterized by severe pain and tenderness in both lumbar regions during the first attack and in the right lumbar region during a second attack. They were accompanied by profuse vomiting, severe headache, slight fever and leucocytosis (as high as 28,000).

Urinalysis.—Spec. gr., 1.018; marked trace of albumin, hyaline, granular and epithelial casts; a few red cells and some hemoglobin. The last two were never observed previous to the onset of abdominal pain.

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8. Deutsches Arch. klin. Med., 1905, lxxxiv, 498-517.
10. Virchow's Arch. f. Path. Anat., xx, 205.

On the morning of October 6, having retired the previous night in an apparently normal state of health, the patient was awakened from sleep at about 6 o'clock by a severe pain in the left upper quadrant of the abdomen. The pain was of a stabbing rather than of a colicky character. It was so severe as to cause the patient to throw himself about in a helpless fashion and to cry out loudly. The pain was confined to a rather small area in the left anterior lumbar region, below the twelfth rib, and from there radiated towards the median line in front. There was no radiation along the course of the ureter, to the penis, the scrotum or the thigh. He vomited profusely and complained of severe occipital headache.

Examination showed a very well developed and well nourished man. The abdominal wall was flat and soft. The pain in the region of the left kidney was increased on palpation. Neither kidney could be felt. The peripheral arteries showed a considerable degree of sclerosis. Temperature was 96 F., pulse 100, and of high tension. At 9 o'clock the patient was given ¼ grain of morphin hypodermatically. The pain did not decrease and the dose was repeated at 9:40 a. m. Severe pain persisted until 10 o'clock and then began slowly to subside. Purgatives and copious hot enemata were ordered.

October 7.—Patient had not urinated or had a bowel movement since the onset of the attack. The pain was now referred to as soreness. Vomiting and headache persisted. There was complete anorexia. Temperature, 96 F.; pulse, 90. About 1 dram of turbid urine was obtained by catheterization. This contained much albumin, no sugar, no red cells, a large number of pus cells, no casts.

October 8.—Temperature, 101 F. Patient was placed in the Presbyterian Hospital. Examination now showed evidences of myocardial involvement. There was positive venous pulsation in the neck, palpable tender liver, and edema of the bases of the lungs. Blood pressure registered 210 mm. At the suggestion of Dr. Sippy, 25 ounces of blood were withdrawn from the right arm, reducing the blood pressure one hour later to 190 mm. Croton oil, m. iii, and later m. v, was administered, but without result.

October 9.—Nine drams of urine were obtained by catheterization. This was distinctly sanguineous in appearance, contained much albumin, numerous pus cells, hemoglobin, but no casts and no red cells. Temperature ranged between 98 and 99 F. Leucocyte count was 16,500. In the afternoon marked arrhythmia developed. Patient was very restless, and complained of air hunger. On the evening of the same day, an exploratory operation was decided on and performed under nitrous oxid anesthesia by Dr. J. B. Murphy. The left kidney was brought into view and freely incised at the convex border down to the pelvis. The cut surface of the kidney was exceedingly dry, pale gray in color, and practically bloodless. No calculi were found either in the kidney, pelvis, or in the ureter.

October 11.—Anuria and constipation persisted. Patient was very restless and dyspneic, but still retained consciousness. Exitus took place the following morning, after six days of almost complete anuria.

Autopsy Findings.—Left kidney was normal in size, measuring 11.5 cm. by 5.5 cm., by 4 cm. Capsule stripped readily. The surface was markedly irregular, presenting numerous cicatricial depressions. The greater part of the organ was of a dull gray color with small areas of dark red. The cut surface was exceedingly dry, bloodless and firm in consistency. The middle portion of the organ presented a structureless whitish-gray area. This area was almost quadrilateral in shape and protruded slightly above the cut surface. It measured 7½ cm. in length and extended from the cortex to the pelvis. This enormous infarct, which occupied more than two-thirds of the entire organ, was sharply delineated on either side by a zone of intensely dark red tissue.

The renal artery and its larger branches were isolated and opened. The vessel walls were found thickened. The artery proper, just at its bifurcation, contained

an adherent red thrombus. This extended into the smaller branches and was continuous with the adherent white thrombi. That these continued into the smaller branches was demonstrated by sectioning the kidney. The right kidney was very small, measuring 7 cm. by 4 cm. by 2 cm., and markedly irregular. The upper third of the kidney was occupied by a large infarct, which had the same dull gray appearance and was sharply delineated from the rest of the kidney tissue. There were also small cortical infarcts. The pelvic fat was excessively developed, and involved the greater part of the organ. The right renal artery showed a still more pronounced thickening of its walls. At one point it presented a marked constriction, the lumen measuring not more than 1 mm. in diameter. The artery and its larger branches were plugged with adherent red and white thrombi.

Summary.—In this case, then, we are dealing with an arteriosclerotic individual, 44 years old, in whom no valvular lesion could be detected at any time. In the history of this patient we have to consider three distinct events manifestly dependent on a common cause: 1. Two years ago, gangrene of the left foot, preceded by severe cramp-like pains. This was soon followed by thrombosis of the vessels of the extremity with sepsis and metastatic foci in the lungs. At this stage there appeared albumin and casts in a previously normal urine, but no blood. 2. Eighteen months later the patient had two attacks of pain in the lumbar regions. Each attack was apoplectiform in onset and accompanied by the synchronous appearance of red cells and hemoglobin in the urine. 3. Two months later occurred a third attack, which was very much more severe and proved fatal. The pain was this time localized in the region of the left kidney. There was an almost total suppression of urine. The latter contained much albumin and hemoglobin. While it is deplorable that the heart could not be obtained for examination, I feel that we can safely rule it out as the cause. For, on the one hand, as was mentioned before, no symptoms of valvular disease were present. On the other hand, a ready explanation was furnished by the condition of the renal arteries. Thickening of the vessel wall and gradual narrowing of the lumen, with consequent slowing of the blood current, induced thrombus formation and its result, infarction. Undoubtedly the same process was responsible for the gangrene of the left foot.

Points of Special Interest in the Last Attack.—(1) Sudden onset. Pain at its acme from the onset and subsiding gradually. (2) Pain increased on palpation and deep breath. No radiation along the course of the ureter, nor toward the penis, scrotum, or thigh. (3) Almost complete anuria, the patient having passed not more than two ounces of urine in six days. (4) Absence of erythrocytes and casts in the sediment, marked albuminuria and presence of hemoglobin. (5) Constipation so obstinate that it could not be overcome by heroic doses of elaterin and of croton oil. (6) Absence of marked uremic symptoms.

GENERAL SYMPTOMATOLOGY.

As we have seen from the cases cited, the symptoms are not many nor are they constant. They can be best discussed under two headings: (1) Local symptoms, (2) accompanying or general symptoms.

Local symptoms are directly due to the infarction. These are pain and changes in the urine. Pain is the most important and constant sign. Three factors at least may contribute to the production of it: (1) Insult to the renal plexus; (2) perirenal inflammation or inflammatory reaction, and (3) tension on the kidney capsule. In most cases the pain is of great intensity and suggests renal calculus. It differs from the latter, however, in that it is not colicky, but is described by patients as stabbing or burning. Furthermore, it is not intermittent. The pain of renal infarct is at its acme from the onset, is continuous and subsides only gradually. It is increased by palpation, cough, deep breathing, change of posture; in other words, by movements of the affected organ. Schmidt, in his careful study of three cases, found that pain was somewhat relieved when patients lay on the affected side; in other words, by putting the kidney at rest. As to localization, this was in all cases in the region of the affected kidney. It is important to remember that the pain is confined to the kidney region proper and does not radiate along the course of the ureter or towards the genitalia.

With regard to urinary changes nothing pathognomonic was observed. Suppression of urine, which in mild cases may be followed by a transient polyuria, or total anuria, may take place. The latter was observed in cases of bilateral infarction. Albuminuria is the most common finding, and its appearance in previously normal urine, especially if associated with pain, is suggestive. Hemoglobin was the next most constant finding. Red cells were not as frequently found and then only in small numbers. Casts were absent in all but one case. Their absence may be due, as Schmidt suggested, to complete arrest of circulation in the affected area, the products of necrosis remaining *in situ*.

Accompanying or General Symptoms.—These are either due to the toxemia of renal insufficiency or are induced reflexly. The following were observed: Vomiting, collapse, severe headache, constipation, cardiovascular symptoms, in some cases leucocytosis and slight fever. Vomiting may be an early and a very distressing symptom. It is due, in Schmidt's opinion at least, to tension on the renal capsule rather than to uremic intoxication. The early onset and rather marked absence of other uremic symptoms seem to support his view. Cardiovascular phenomena are important because they point to a source of embolism and

suggest the possibility of infarct formation. According to Schmidt, high blood pressure speaks against an infarct. No observations on this point were made in the cases reported. In my case the blood pressure was 210 mm. and was but little affected by removal of 25 ounces of blood, a circumstance which casts suspicion on the above statement. Leucocytosis and slight elevation of temperature, observed in some of the cases, may be due to absorption of the necrotic renal tissue.

DIFFERENTIAL DIAGNOSIS.

It is hardly necessary to emphasize the difficulty, often impossibility, of recognizing the condition, even in the presence of marked symptoms. To quote Leube, "The diagnosis can rarely be made. The condition may be surmised with some probability when, in the presence of a possible source for the formation of emboli and infarcts, sudden pain develops in the region of the kidney, and albumin, blood or morphologic elements indicating nephritis appear in the urine."

In the diagnosis of renal infarct we must first exclude all conditions outside of the kidney and ureter capable of giving rise to sudden and severe abdominal pain. Among the most important are: gastralgia, perforative peritonitis, acute ileus, gallstones, embolism of the mesenteric artery, lead colic, and gastric crises. The consideration of the differential points in these conditions would take us too far from our subject, and, as they are, furthermore, familiar to every clinician, their discussion will be omitted here. In the second place, we must consider all conditions capable of giving rise to symptoms of renal colic or severe renal pain, such as (1) torsion of the ureter in a wandering kidney, (2) paroxysmal exacerbations of chronic nephritis, (3) calculus colic, (4) pseudocolic, which may be caused by (a) plugging of the ureter with tuberculous or neoplastic débris, blood clots, hydatids, (b) by obstruction due to catarrh of the ureteral mucosa, and (c) by functional spasm of the ureter.

It is important to decide first whether the pain is of renal or ureteral origin. The following conditions speak for renal origin: 1. Pain confined to kidney region proper. 2. Kidney tenderness. 3. Continuous character of the pain. 4. Albuminuria, casts, etc., in the sediment. The following point to ureteral origin: 1. Radiation of pain along the course of the ureter. 2. Tenderness in the course of the same. 3. Intermittent character of pain. 4. Presence of hydronephrosis.

Having established a renal cause of the pain, we still have to consider the following possibilities: (1) Twisting of the ureter of a wandering kidney; (2) acute exacerbation of chronic nephritis; (3) renal infarct. While the differentiation is not easy, the following points may be of value

as pointing to the diagnosis of infarct: (a) sudden onset of intense pain while the patient is at rest; (b) sudden appearance of albumin in the urine; (c) kidney tenderness; (d) presence of a valvular lesion of the left side of the heart.

Marked hematuria speaks against infarct and for nephritis, or malignant tumor. In the latter case, a palpable mass is frequently present at this stage. High blood pressure and marked uremic symptoms are more common in nephritis. Pain is never as severe in nephritis as it is in infarct.

In conclusion, it may be said that, while attention to the above symptoms may enable one occasionally to recognize a renal infarct in a marked case, the condition must still belong to the category of conditions best diagnosed postmortem.

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EFFECTS OF PROLONGED ADRENALIN MEDICATION ON THE HUMAN CIRCULATORY ORGANS.

WITH CASE REPORT.

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Adrenalin, once a drug of promise, is now in such general use and is employed in so many varying conditions, often with the greatest benefit, that it is important for us to learn all we can in regard to its deleterious effects on the human body. The work of Takamine, Cushny, Abel and many others has made us fully conversant with its physiologic action. Its value as a therapeutic agent no one can deny, though we, in common with many others, think that it is too generally administered, and in many instances without even a theoretic basis for its exhibition.

Physicians, and notably the resident physicians of hospitals, entertain very erroneous ideas as to the effects of the drug. Thus, it is generally supposed to cause a marked increase in blood pressure soon after its hypodermic administration. An injection controlled by a sphygmomanometer on the arm will, however, soon dispel this idea and demonstrate that in order to produce this condition adrenalin must either be thrown directly into the blood stream or given as an intramuscular injection, and that even then the elevation of the blood pressure is often slight and always very transitory. Increase of blood pressure is rarely produced when the drug is given subcutaneously, and in such instances the psychic effect of the injection should be taken into account.

Thus far the results of the drug in protracted, large or poisonous doses have been chiefly, if not exclusively, studied on animals, and those who have followed the work of Pearce, Adler, Loeb and numerous others can not fail to be impressed by the possible danger which may result from the persistent use of this powerful agent.

It has been definitely shown that in many but not in all instances the injection of adrenalin solutions into the circulation of animals causes lesions of a serious nature in the vessels. It has also been demonstrated that in many cases the degree of the lesion is not dependent on the size of the dose, nor yet on the relative body weight of the animals. Sometimes very minute amounts cause very serious changes, while at

other times very large doses produce no effect whatever. More recent communications show us that we have probably overestimated the effect of this drug in causing vascular lesions, since quite similar changes have also been reported in control animals. We have found from our experiments that an immunity is developed in animals as in most drugs of this class. This enables them to withstand very much larger doses than could previously be borne if the injections are continued for a long time. Thus, we now have a rabbit weighing 1800 gm. that outlives 50 drops, intravenously, of a 1:1000 solution.

As to the manner in which the lesions are produced, it was at first thought that the great elevation of the blood pressure which sometimes takes place on the administration of the drug caused an actual laceration of the walls of the vessels, a true mechanical lesion. In some cases this is true, but in most instances in which lesions occur it acts in some other way, causing the appearance of degenerative or necrotic foci, especially in the media of the vessels.

Attempts have been made to reproduce the changes which occur in human arteriosclerosis experimentally, and for a time it appeared that we could cause lesions like those seen in true arteriosclerosis. Further study has convinced us that the lesions produced by adrenalin in the vascular system of experiment animals are not those of true arteriosclerosis as seen in man. The interpretation of this discrepancy admits of at least two explanations; one, which now seems the more probable, is that adrenalin does not cause lesions in animals like those of arteriosclerosis in man; the other is that the tissues of the arterial wall react differently in animals than in man.

It, therefore, seems very important that we place on record the following case in which adrenalin was administered for over three years, the drug being given daily, intramuscularly, and in large amounts, varying from 10 to 120 minims per dose. Perhaps it is well, by way of justification, to state that our case was a most persistent one of bronchial asthma in which anything which would give even momentary relief was justifiable.

History.—Mrs. M., 35 years old, houseworker, born in Austria; thirteen years in the United States. Admitted May, 1904, and died in April, 1907. Family and personal history was negative, except for one miscarriage at the third pregnancy. No specific history; no neurotic disposition, except for worry and excitement brought on by marital troubles.

Present Illness.—Began in December, 1901, with a severe cough, the result of a cold contracted while exposed to rain and snow. This cough continued, accompanied by dyspnea, until 1904, when the condition became unbearable. Various drugs that were tried proved of no avail.

Status Præsens.—Neck short, muscles stand out prominently, especially with inspiration. Patient has anxious look, breathes through the mouth, gasping for breath. Examination of nose disclosed the presence of about ten small polypi. Heart: Apical impulse not visible; heart impulse not felt. Very difficult to make out cardiac dulness. Auscultatory percussion gives normal cardiac outline. Sounds normal at all ostia. Pulse, 90 per minute, regular, equal, fair tension, vessel wall moderately thickened. Blood pressure: Systolic, 130; diastolic, 85. Lungs: Expiratory period very much prolonged. Mouth breather. On palpation, here and there fremitus with inspiration and expiration. Percussion: Right anterior, below clavicles, resonance is impaired, rest of lung wooden. Auscultation: Inspiration short, harsh, stopping suddenly, followed by a long expiratory period which is accompanied by wheezing, whistling, and moaning sounds. The breathing can be heard at a distance from the patient. Respirations, 17 per minute.

Treatment.—Although various other methods of treatment were instituted, including the removal of the polypi, only the adrenalin medication will be detailed here. The drug was used intramuscularly in 1 to 1000 solution; its effects observed, and if no relief followed, another injection was given. As a rule, one syringeful was enough to cut short an attack; occasionally, however, even two injections would not suffice, and there are records showing the exhibition of as much as 120 minims of the drug. The dosage varied with the severity of the attacks. It was possible to curtail some seizures with 10 minims. The long time of the patient's stay in the hospital gave ample opportunity for observing the effects of adrenalin chlorid on the circulatory system, and the observations on this system only will be given here. Its effects, as far as the attacks are concerned, can be stated in a few words: All symptoms of an asthmatic attack were relieved. The pulse could often be felt more distinctly after using the adrenalin than before, whereas, during the asthmatic attack it was barely perceptible. A few minutes after the administration of the drug, the arterial pressure as observed during one of the attacks rose and remained elevated for about ten minutes. A reading was as follows: Systolic pressure, 120; diastolic pressure, 85. After the injection of 20 minims of adrenalin, the pressure was again ascertained without removing the cuff from the arm and gave the following results: Systolic pressure, 145; diastolic pressure, 100. The numerous repetitions of the injections—the patient having received during her three years' stay in the hospital no less than 2,000—did not permanently alter the blood pressure, as readings shortly before death show that the pressure remained at about the same level during both free and seizure periods; in fact, one could not tell from a clinical examination shortly before death that the heart and vascular system had sustained permanent injury from the enormous quantity of adrenalin chlorid injected during these three years. If we allow only 10 minims to a dose (the smallest injected), the total amount of the drug given was 44 ounces.

Summary of Autopsy Findings.—Inspection: Adult woman. Moderate cyanosis of the skin. Purpuric blotches over entire surface, varicosities over calves. Face congested, pupils dilated, neck and lips swollen. Slight anterior kyphosis of spinal column. Abdomen distended. Section: Muscles deep red, natural. Panniculus deeply colored, abundant. Veins widely dilated, arteries large, thickened. Mammæ well developed. Precordium covered by emphysematous borders of lung. Pleura and pericardium negative. Heart small, right ventricle collapsed, empty. Left ventricle contracted, empty. Aortic segments slightly thickened; marked cupping of sinuses and funnel-shaped extension into coronaries; other valves normal. Heart muscle soft, turbid, friable, moderate quantity of epicardial fat, right auricle shows great distension. No thickening of endocardium. Coronary arteries markedly thickened, not calcified. Weight

of heart, 8 ounces. Hypertrophy of adenoids of tongue and pharynx, all neck structures edematous, including folds of larynx. Thyroid large, natural; no thymus. Lymph nodes of neck enlarged, anthracotic; show healed tubercles. The right innominate and subclavian arteries at their origin from the arch show slight dilation. The left carotid shows slight spindle-shaped dilation in mid-portion. Dilated arteries show roughening of intima and aorta somewhat irregularly thickened. Small trunks of neck show slight atheroma. The larynx and large bronchi contain tenacious mucus; mucous membrane atrophic. Mucous membrane of medium sized and small bronchi congested. Mucoid spirals abundant in finer air pasages. Lungs show emphysema, edema and congestion of posterior portion. Pulmonary vessels show no change. Peribronchial lymph nodes show anthracosis and healed tuberculosis. Liver large; a few isolated areas of necrosis. Gall bladder and ducts negative. Spleen, enlarged, deep purple and soft. Stomach, negative. Small and large intestine negative. Appendix negative. Mesenteric lymph nodes show calcification and necrosis, old. Tissues about pancreas show chronic inflammation and old areas of fat necrosis. Pancreas, deep purple in color, infiltrated in every direction by recent hemorrhage; marked arteriosclerosis of pancreatic vessels, especially of pancreatica magna, but no rupture present. Adrenal bodies large; no gross abnormality. Kidneys, congestion and edema; arterial thickening; parenchymatous degeneration; moderate interstitial nephritis. Internal genitals, negative. Bladder, negative. Aorta and large trunks of abdomen and pelvis present a moderate diffuse thickening with occasional minute areas of atheroma without calcification in the intima. Brain, moderate edema of membranes; vessels at base show slight thickening; otherwise negative.

Anatomical Diagnosis.—Bronchial asthma, terminating with pancreatitis hemorrhagica, complicated by parenchymatous nephritis, pulmonary edema and congestion.

Microscopic Examination.—Brain and medulla: Corpora amylacea in considerable numbers beneath membrane, notably along floor of fourth ventricle. Congestion of minute vessels and occasional slight hemorrhages by diapedesis. Occasional ganglion cells show atrophic changes.

Lung: Congestion in posterior portion, marked emphysema. Smaller bronchi surrounded by inflammatory thickening and tubes filled by compact mucus in the meshes of which are many eosinophilic leucocytes. Large vessels show moderate subendothelial hyperplasia and occasional hyaline degeneration of media.

Liver: Parenchyma show pronounced albuminous degeneration, with moderate fatty infiltration. Slight brown atrophy, with ferruginous pigmentation in places. Supposed necrotic areas show beginning fibroid replacement of parenchyma, general edema. Blood vessels negative.

Pancreas: Recent extensive areas of capillary hemorrhage, considerable quantities of old iron pigment, probably representing old areas of hemorrhage, extensive necrosis of parenchyma, both in acini and in bodies of Langerhans. Extensive necrosis of pancreatic ducts. No changes in the interstitial tissue.

Kidneys: Extreme acute parenchymatous degeneration with extensive desquamation of tubercular epithelium. Hyperemia of vessels, with hemorrhage by diapedesis. Hyaline degeneration in small foci in media and subendothelial areas.

Spleen: Congested lymphoid hyperplasia. Hyaline degeneration affecting media of many blood vessels.

Lymphnodes: Lymphoid hyperplasia of moderate degree. Healed tuberculosis in bronchial nodes. Hyperplasia of lymphatic endothelium and general anthracosis. No vascular lesions noted.

Uterus: Endometrium thickened. Marked proliferation of subendothelial layer and of adventitia and of most blood vessels; no changes of media.

Ovary: Vascular changes as found in uterus, otherwise tissue is normal.

Thyroid gland: Entirely normal, but shows evidence of excessive activity.

Adrenal glands: Pronounced fatty infiltration of cortex. General hyperplasia of cells in medulla, particularly of those bordering on the large venous sinuses. Marked congestion of blood vessels in medulla.

Heart: Considerable quantity of epicardial fat with infiltration of stroma. Marked capillary hyperemia. Marked brown atrophy with fatty degeneration and acute parenchymatous degeneration. Many atypical karyokinetic figures in the nuclei of muscle cells. The coronary vessels show marked thickening of subendothelial layer, with marked hyaline degeneration of both the muscle cells and the hyperplastic connective tissue. Occasional circular foci of necrosis in media and subendothelial tissue.

Aorta: Endothelial layer broken and eroded in many places. Occasional areas of endothelial hyperplasia. Minute areas of necrosis, oval or spherical in shape, chiefly in subendothelial layer, and involving both white fibers and yellow elastic, as well as the muscle fibers. In a few areas very slight calcareous infiltration is demonstrable, but fatty disintegration can not be shown. No distinctly evident lesions in vasa vasorum.

Main trunks (femorals and carotids): The nodular subendothelial thickening and necrosis is very marked in trunks of this class, and in most of them the internal elastic layer is broken in many places. The necrotic process in the media is also much more marked than in either the larger or the smaller trunks. The vasa vasorum show no very apparent changes.

Small trunks: Some of these vessels show marked hyaline degeneration, with resulting necrosis in the media, the foci of subendothelial necrosis mentioned in the other vessels is not present.

The visceral alterations are predominatingly of an acute parenchymatous type and are apparently of recent origin for the greater part. Some of the organs, notably the liver, heart and lungs, show also the changes resulting from chronic passive congestion, probably of considerable standing. The lungs show, in addition, the typical changes of a chronic bronchial asthma. The pancreatic lesion apparently originated some weeks before death, finally terminating with an acute diffuse capillary hemorrhage and resulting necrosis. It does not appear probable that these changes in the pancreas are to be directly attributed to the long continued use of adrenalin, although this explanation is to be considered. The alterations in the medulla of the adrenalin bodies may be etiologically related to the adrenalin medication.

The most striking lesion found in the aorta and large trunks is preeminently a type of focal necrosis, which we believe to have been entirely separate and distinct from the ordinary changes of arteriosclerosis which are also manifested in lesser degree in the same vessels, and which are probably due to the asthma *per se*. This focal necrosis, and especially that involving the media, is quite similar to that produced in experi-

mental adrenalin poisoning, and we believe it to be due to the prolonged and free administration of this drug in this particular case.

While admitting that the necrotic changes in this case were due to the adrenalin medication, we do not believe that they are in any sense to be taken as contraindicating a moderate and temporary utilization of adrenalin in appropriate cases. On the contrary, we believe that the relatively slight degree of these changes in a case in which the drug was used so freely and for so long a time indicates that in ordinary cases it may be used with relative impunity in amounts sufficient to produce therapeutic results.

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METABOLISM EXPERIMENTS IN ARTIFICIAL NUTRITION,

WITH SPECIAL REFERENCE TO THE HYPODERMIC METHOD.

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The whole subject of artificial nutrition presents great fascination for internists both from the theoretical and the practical point of view; for the idea of nourishing the body, meeting its physiologic needs, so to speak, without the knowledge or consent of the patient, when occasion arises, has seemed an end highly desirable at times.

The conditions under which this would be of value are, of course, various, and need not be discussed here beyond pointing out the fact that in cases of subnutrition which, in part or whole, preclude the natural method of maintaining the physical economy, some such method would often be of the greatest use. Thus, it is indicated in acute gastroenteritis in children, in marasmus, in strictures of the alimentary tract when the patient comes under observation in a condition too weakened to allow of an operation for the time being, etc.

With the introduction of the stomach tube in 1870, by Kussmaul, we were enabled to nourish certain cases in which forced feeding is a necessity, despite the existence of a fairly normal digestive tract, as in cases of mental disease. Later, the rectum as an auxiliary stomach came into general use. Attempts were made to give nourishment by means of hypodermic food solution, or by the intraperitoneal route. Of course, any form of artificial feeding, to be entirely sufficient, has to meet the actual needs of metabolism. The requisite amount of nitrogen and heat units must be furnished or the organism will be forced to run at an economic loss, resulting in loss of flesh and strength.

Our knowledge of these requirements has been greatly increased since Voit and his pupils determined the average amount of the different food elements used by individuals doing light or heavy muscular work and maintaining their body weight. According to this standard, a person of average weight (70 to 75 kilos) needs about 118 grams of protein, 56 grams of fat and 500 grams of carbohydrate, with a total fuel value of 3,000 large calories, although Voit[1] was able to establish nitrogenous

1. Voit: Ztschr. f. Biol., xxv, 261.

equilibrium for a short time in one patient who took only 8 grams of nitrogen, which corresponds to 48.5 grams of proteid, for a day's ration. This, however, he considered far too small an amount to maintain nitrogen equilibrium for any length of time.

Chittenden[2] became convinced that a low protein diet could be maintained, not only without detriment to the individual, but to his actual advantage, provided sufficient heat units were furnished by the other food elements. This he proved to his satisfaction in his interesting experiments on athletes, soldiers and students, representing individuals doing, respectively, severe, moderate or light muscular work. He found that the average requirements per kilo of body weight were as follows: 0.12 gram nitrogen, representing 0.65 gram protein per kilo of body weight, with a total fuel value of the food represented by 32 calories per kilo, made up largely of fats and carbohydrates.

This, therefore, can be taken as representing the minimum food requirements necessary to maintain not only the nitrogenous equilibrium, but the general physical condition and body weight of persons who are at work, while at rest the calorific value of the food can be reduced to about 25 calories per kilo.[3] Any form of alimentation to be complete must meet these requirements, although under pathologic conditions one would be satisfied with something less than the ideal.

With the older standards, the problem seemed out of reach, but with the introduction of these lesser requirements artificial nutrition seems a much more promising field, and it was with this in mind that the following studies were undertaken.

In approaching this subject, two questions naturally present themselves: (1) Is the method ordinarily in use capable of accomplishing satisfactory artificial nutrition? (2) If not, wherein does it fail, and what other methods offer a possible solution of the difficulty?

In rectal feeding, the most common method of artificial nutrition, we have these questions to answer. As to whether this form of feeding is capable of supplying the needs of metabolism, if one regularly weighs these patients daily or even watches them clinically from day to day, the answer must be, No. They do not thrive. This, I think, will be borne out by the clinical experience of most of us. Rectal feeding is, at best, a poor substitute for stomach feeding, although, of course, patients differ, and in some it seems more successful than in others. It must be borne in mind, however, that most people can go without food very

2. Chittenden: Physiologic Economy in Nutrition.
3. Lusk: Jour. Am. Med. Assn., xlix, 201.

comfortably for a number of days, provided they are supplied with water, but after a certain time, whether on rectal feeding or not, they often seem to retrograde suddenly.

In order to answer the question as to the specific cause of failure in most of these cases, one must study the metabolism and carefully estimate the intake and output, with especial reference to the nitrogen, as the best index of metabolism. The following figures show the results of metabolism in three cases of rectal feeding and may be taken as fairly typical of a large class, as they occurred in one of the large city hospitals, under nursing conditions which are as good as can be found. If these results are true under favorable conditions, what can be expected under ordinary conditions, outside the hospitals?

It can not be said that more satisfactory results may not at times be obtained by rectal feeding. But these cases probably represent the average. In all of them the usual precautions were taken: the colon was cleared daily, the injections were given high up, and the report, in every instance, was that they were "well retained." The entire twenty-four-hour urine, all results of rectal irrigation, and all stools were saved, and, together with a sample of the food, were sent to the laboratory daily. It seemed a work of supererogation to estimate the intake and output of nitrogen, for the results of the cleansing enemata were evidently an almost clear return of the nutrient material, and one could tell by inspection that little, if anything, was being absorbed. The following figures, however, represent the daily nitrogenous balances, estimated by the Kjeldahl method, and show graphically the failure of this method of nutrition; since in these cases at least nitrogenous equilibrium was far from being maintained.

CASE 1.—*Gastric Ulcer.* Man, aged 46, weight 115 pounds.

History.—Patient had been on rectal feeding three days before the test was begun. The nutrient fluid consisted of peptonized milk and eggs, 1240 c.c. per twenty-four hours, with a total nitrogen value of 11.78 grams.

NITROGENOUS BALANCE.—FIRST DAY.

Total intake of food nitrogen	11.78 grams.
Total nitrogen output (urine, 4.74 grams; feces, 23.95 grams)	28.69 grams.
Total loss of nitrogen, 24 hours, output in excess of intake	16.91 grams.
Total loss in body weight	1 pound.

NITROGENOUS BALANCE.—SECOND DAY.

Total intake of food nitrogen	12.40 grams.
Total nitrogen output (urine, 11.5 grams; feces, —; irrigation, 22.72 grams)	34.22 grams.
Total loss of nitrogen, 24 hours, output in excess of intake	21.80 grams.
Total loss in body weight	2 pounds.

NITROGENOUS BALANCE.—THIRD DAY.

Food formula changed this day to peptonized milk, glucose and water, 2,000 c.c. in all for the twenty-four hours.

Total intake of food nitrogen..... 7.20 grams.
Total nitrogen output (urine, 9.58 grams; feces, 6.43 grams) .....16.01 grams.
Total loss of nitrogen, 24 hours, output in excess of intake... 8.81 grams.
Total loss in body weight ..... 2 pounds.

In this balance for the third day we see for the first time that something was actually absorbed by the rectum, or else retained, for the food intake was 7.2 grams nitrogen, and the fecal nitrogen equals 6.43 grams, leaving an absorption balance of + 0.67 gram nitrogen, which is, of course, so small as to amount to nothing from the standpoint of nutrition.

(NOTE.—The probable explanation of the fact that on the first two days the nitrogen in the stools and irrigations was greatly in excess of that artificially injected in the enemata is that material from previous days was retained and expelled along with the stools passed on test days.)

CASE 2.—*Gastric ulcer.* Man, aged 27.

Food: Peptonized milk and eggs.

NITROGENOUS BALANCE.—FIRST DAY.

Total intake of food nitrogen ..... 6.37 grams.
Total nitrogen output (urine, 15.52 grams; feces, —; irrigation, 6.89 grams) .....22.41 grams.
Total loss of nitrogen, 24 hours, output in excess of intake...16.04 grams.
(Patient could not be weighed.)

NITROGENOUS BALANCE.—SECOND DAY.

Total intake of food nitrogen ..... 6.35 grams.
Total nitrogen output (urine, 15.60 grams; feces, 9.06 grams) .....24.66 grams.
Total loss of nitrogen, 24 hours, output in excess of intake...18.31 grams.

CASE 3.—*Postoperative perforating gastric ulcer.* Man, aged 23.

Food formula, peptonized milk and egg, with panopeptone. Patient had been on this several days, when test was made only on one day, so that it is rather incomplete. Daily volume, 712 c.c.

Total intake of food nitrogen ..... 4.69 grams.
Total nitrogen output (urine, 19.04 grams; feces, 9.84 grams) .....28.88 grams.
Total loss of nitrogen, 24 hours, output in excess of intake...24.19 grams.

Little comment is needed in addition to a glance at the figures presented to prove the inadequacy of rectal feeding in these cases, and it may be assumed that in the vast majority of cases the results are little, if any, better.

The minus nitrogen balance varies from — 8.81 grams to — 24.19 grams, and is accompanied by a steady loss of weight in the first case (the only one weighed), apparently also in the others.

In a review of the literature on this subject, the only paper found to approach it from the standpoint of exact metabolism was by Edsall and Miller,[4] who investigated two cases with rather better results, so far as

4. Wisconsin Med. Jour., 1903, i, 87.

concerned actual absorption of the nutrient mixture of peptonized milk and eggs by the intestinal wall, but the nitrogenous loss averaged 11.8 to 10.9 grams nitrogen for the test period of six days. From clinical observation, however, and from the foregoing cases, the conclusion may be drawn with considerable certainty that rectal alimentation, as ordinarily practiced, is of little or no value in most instances, while in some it may prove harmful by using up the patient's strength. Of course, it has been proved that water is well absorbed by the rectum and that this method of introducing water is of extreme value.

Having satisfied ourselves of the foregoing facts, the next question which naturally arises is: Can nutritive equilibrium be maintained more satisfactorily by any other artificial means?

Many investigations have been undertaken to determine the effect of intravenous injections of various foodstuffs in solution. Although the prime object of most of such attempts has been to study the effects of these substances on the organism, incidentally side lights have been thrown on the subject of nutrition, although mostly in a negative way, as substances so injected have been proved unsuitable for use in artificial nutrition, either because of their toxicity or because they are immediately excreted for the most part.

Leaving out of consideration intraperitoneal nutrition as unsuitable and impracticable for continued use, one naturally turns to the problem of artificial nutrition by the hypodermic injections of foodstuffs. With the introduction of Chittenden's lowered food requirements it occurred to the writer to attempt to prepare an artificial, soluble food, containing the precise nutritive requirements for an individual calculated on Chittenden's figures; to inject it into the subcutaneous tissue and determine the nitrogen balance day by day, to see if the requirements of the body were being met, and the body maintained, not only in nitrogenous equilibrium, but also in weight.

The literature on this subject is surprisingly scanty. There are no articles accessible to the writer in which the subject has been approached from the standpoint of metabolism. What has been done may roughly be divided into clinical inquiries and laboratory experimentation. The clinical observations have been of the crudest sort, and the reports contain almost no data concerning the cases or, at best, very insufficient data. Whittaker,[5] in 1877, reported the case of a man nourished for six days by subcutaneous injections of milk, extract of beef and later cod liver oil; but from the article there is no proof that the man was nourished

5. Am. Jour. Med. Sc., April, 1877.

in the real sense of the word, for no mention is made of body weight during this period, of the total amount of food injected, nor of the excretions, and we know that a patient can survive a short period of starvation with comparative ease. Kreng[6] injected 15 to 20 c.c. of olive oil hypodermically for twenty days and succeeded in maintaining the patient's weight (?) and strength.

Pick[7] quotes a case from Whittaker, who nourished a girl suffering from gastric ulcer, with a weak pulse and high temperature, for four days by hypodermic injections of milk and beef-blood, with "great increase in weight and strength, after which period the patient was able to take nourishment by mouth and the temperature fell." The dose of milk was a dram at a time, which is an absurdly small amount relative to the nutritional requirements, and makes one extremely skeptical of the results as recorded.

Leube[8] injected a 20 per cent. sugar solution and found that it was well borne if only a few cubic centimeters were given at a time, but the limit of absorption was 15 to 20 grams of sugar in the twenty-four hours, all beyond this being excreted in the urine.

A more recent report by Barker[9] speaks of the successful use of a 5 per cent. glucose solution in normal salt solution; this gives a solution which has the same freezing point as normal blood, — 0.56° C. He used it in preparing some patients for operation, and only in one instance were the injections followed by glycosuria, although he fails to state the amounts injected, and gives no weights or metabolism data. This was tried on one case of marked asthenia from pyloric stenosis, but without success, as the patient died of exhaustion. On the other hand, most other experimenters agree that the usefulness of glucose is very slight, as it is so promptly excreted when given in nourishing amounts, while in the hands of some it has caused necrosis at the point of injection.

Turning to the purely experimental aspect of the subject, we find more data, but the results have been largely negative or unsatisfactory.

Of the substances tried, fat, in the form of oil or butter, has been most frequently used. Without going into the details of the various experiments, we may take Henderson and Crofutt's[10] statement as embodying the latest and most satisfactory results of experimentation along this line. They say: "Oil injected subcutaneously is readily and widely distributed through the subcutaneous tissue. It is not transformed *in*

6. New York Med. Jour., March, 1876.
7. Deutsch. med. Wchnschr., 1879, v, 31.
8. Verhandl. Cong. innere med., Wiesbaden, 1895, xiii, 418.
9. Am. Med., 1905, ix, 234.
10. Am. Jour. Physiol., 1905, xiv, 193.

situ into adipose tissue. The tissues react to its presence as to any non-irritating, foreign substance. In the blood and lymph it does not appear in detectable amounts, and, while the oil is ultimately absorbed and utilized in metabolism, the process is one of extreme slowness. Oil injections in any moderate amount are, therefore, practically without nutritive value."

Winternitz[11] found that only 2 to 5 grams per day were utilized and that for subcutaneous nourishment it was not of practical value.

When we come to consider the availability of protein for subcutaneous injection, we are met by a variety of opinions. Eichorn,[12] in a series of experiments, used cow's milk (1/3 water), "Sanders peptone" and egg albumin. He concluded (1) that they are wholly absorbed, (2) that egg albumin often leads to abscess formation, (3) that cow's milk, diluted, takes the longest time for absorption, (4) that there is no local reaction from 20 grams of peptone. He also injected five dogs with albumin, olive oil, cod liver oil, almond oil and sugar solution, and states that most of the dogs maintained their weight. Few details of the experiments are given and there are absolutely no metabolism figures; the whole subject is very incompletely treated.

In another series of experiments, he used defibrinated pigs' blood and calves' blood, but without satisfactory results, and concluded his article by saying: "When we look at the results of subcutaneous injection of foods, we can assume that materials which do not inflame the cellular tissue when injected can be used for a while, often to advantage, to save life or postpone death by starvation."

Leube[13] found that the injection of 18 grams of "somatose" into a dog caused marked disturbance of well-being and led to albuminuria, due to renal irritation (see also results of somatose injections in these experiments).

Ewald,[14] discussing the subject, dismisses with a word albumoses and peptones as poisonous and useless.

Leube,[15] in a later article, speaks much in the same way, but suggests that possibly albumin, in the form of an alkali albuminate or syntonin, might be of use, although he had not tried it (see second experiment in this series).

11. Winternitz, Ztschr. f. klin. Med., 1903, l, 80, 101.
12. Wien. klin. Wchnschr., 1881, 918.
13. Verhandl. Cong. innere Med., Wiesbaden, 1895, xiii, 418.
14. Cong. internat. de méd., xiii, Paris, 1900.
15. Ibid.

Four years ago Trolldenier[16] used an albuminous substance intermediate between the peptones and albumoses. Of this he gave 100 c.c. (10 per cent. solution) to each of several dogs. In summarizing his results he says that the dogs maintained their weight; that the urine showed albumose; that the injections were painful, and that abscesses developed at the point of injection. It is hard to believe that these dogs could possibly have kept their weight on the amount of protein which Trolldenier gave them, as it has been found that a dog needs at least 0.3 gram nitrogen per kilo to maintain nitrogenous equilibrium, while these dogs received but a fraction of that, about 0.2 gram.

From this brief review of some of the most important contributions to the subject, it can readily be seen that the problem of providing sufficient food to an animal by injection and at the same time approximately maintaining its nitrogenous equilibrium, to say nothing of its weight, is a most difficult one. It was felt, however, that it would be exceedingly desirable to attempt it, inasmuch as, if successful, some plan might be evolved for artificial nutrition in man, although any method to accomplish this successfully must be both clinically safe and nutritively sufficient, or nearly so, and must rest on the scientific facts of metabolism. Toward this end the following experiments were performed on dogs:

EXPERIMENTS ON DOGS.

Preparation of the Dogs.—As a routine, the dogs were put on the regular laboratory diet and confined in metabolism cages, where all excreta could be saved for analysis. As a rule, the dogs lost a little weight for a few days, and then settled down to almost constant weight from day to day. It was not until this had been accomplished that an experiment was attempted.

In the first attempt a food which was theoretically perfect was prepared from "somatose," representing the protein element in the form of soluble meat peptone, at the dog requirement of 0.3 gram nitrogen per kilo; the remaining requisite number of heat units (on human basis) being made up of glucose in normal salt solution, the whole being sterilized by thorough boiling.

EXPERIMENT 1.—Three preliminary injections were made of this food, the first representing 0.66 gram somatose per kilo, the other two 0.42 gram per kilo each, and the effects were noted. The larger amounts caused marked toxic symptoms, trembling, inability to stand, and rise of temperature, a trifle over 4° F. within four hours. The smaller amounts were better borne, but still gave rise to some toxemia. The urine after the third injection gave a positive biuret reaction, and sugar was also present, but apparently in small amount. After a few days of rest on regular mouth-feeding, a forty-eight hour period was begun with the same food, dividing the twenty-four hour requirement into three injections for morning, afternoon and evening; at each injection an amount of peptone was used equal to 0.5 gram per kilo of weight.

Without going into the details of this experiment, it was seen that the dog showed less and less reaction, although the effects were too severe to constitute a result at all satisfactory from a clinical point of view. The temperature rose

16. Berl. klin. Wchnschr., 1903, xl, 912.

from 2° to 3° F., and the dog became weak and ill, the urine was lessened in amount, contained albumin, peptone, sugar, hyaline and granular casts. The injection fluid collected on the under side of the body and caused marked edema. Between the 10 p. m. and the 10 a. m. feeding of the following day, the dog largely recovered its normal physical condition.

Following the period of injections, the dog passed an excessive amount of urine, probably from the subsidence of the edema, and continued losing some weight, even after it had been on regular mouth feeding again, receiving daily the same amount of food that had maintained it previously at a practically stationary weight. This loss in weight continued for a few days, then the weight remained stationary at a lower level. This, curiously enough, was the rule after most of the injection experiments. These results were not such as were thought worth following up as the toxemia was too marked, and for this reason chemical analyses were not made. Table 1 shows in graphic form the data collected.

TABLE 1.

	Date.	Weight. kilos.	Food Solution. c.c.	Volume Urine. c.c.	Urine. Sp. Gr.	Clinical Notes.
1.	March 30.....	6.43	†	340	1016	Dog well.
2.*	March 31.....	6.66	315	138	1045	Dog weak; some difficulty in standing. Temperature 104.5° F. Edema.
3.*	April 1.....	6.70	315	160	1043	Has had six injections; condition about same; urine contains albumin, peptone, sugar, hyaline and granular casts.
4.	April 2.....	6.03	†	705	1011	Dog fairly well again.
5.	April 3.....	5.86	†	390	1014	Urine: albumin, distinct trace; sugar absent, occasional cast.

* Injection period. † Regular food.

EXPERIMENT 2.—In the second experiment it was thought that possibly an alkali albuminate made from meat would meet the essential qualities of solubility and being capable of sterilization and might also be found to be less toxic than the peptone; this was prepared and diluted with normal salt solution. No account was taken in this experiment of furnishing the required calories, as it was undertaken solely with the view of seeing whether or not such a preparation would be of use.

The results of the injection of the alkali albuminate were most unsatisfactory, causing vomiting, bloody diarrhea, renal irritation, and local necrosis at points of injection.

The meat peptone and albuminate having proved so unsatisfactory, it was thought that possibly the peptone from cow's milk might be better borne, for it was conceivable that some of the toxicity of the meat peptone preparations might have been due to the extractives present.

In order to make this milk peptone, the certified city milk was used, after removing the gravity cream (as we have seen the fats are so slowly and insufficiently absorbed); this was then digested for three hours, by means of dry extract of pancreas with dilute sodium carbonate. The liquid was then sterilized by boiling, strained and put in sterile flasks after removing a sample for nitrogen determination.

EXPERIMENT 3.—For this experiment a small, pregnant dog, weighing 5.19 kilos, was used, and in order to find out at once the toxicity of this milk peptone, rather large amounts were used, equivalent to 0.4 gram nitrogen per kilo, divided into two doses, given twelve hours apart. Following the first injection, the dog gave birth to one normal pup. There were only moderate toxic symptoms, nothing

like as severe as those following beef peptone and albuminate. Although the results with the milk peptone were not entirely satisfactory, it was decided to go ahead, employing a three-day period with this large amount of protein injection. The reason for using so much more than the absolute dog requirement was to determine whether or not it was dangerously toxic, this percentage of nitrogen per kilo being nearly four times that required for man.

In spite of this, it will be seen that the mother lost weight decidedly, and after the first day the temperature rose 2° F. and remained up. Some milk was secreted, but the pup failed to get sufficient nourishment and lost weight steadily. At the end of the third day, the mother was only in fair condition, was considerably poisoned, as evidenced by temperature, malaise and suffusion of conjunctivæ. The pup had lost in weight and strength, so it was decided to stop the experiment and return the mother to regular mouth feeding. This was done at the end of the third day, and, although more milk began to be secreted, the pup was now too weak to get a supply, and died on the fifth day. After the first day, the mother refused all water by mouth, as she was evidently receiving sufficient fluid from the injections.

It will be seen on examining Table 2 from this case, that at the end of the first twenty-four hours, the amount of urine excreted was smaller than normal (the usual occurrence in these cases), but of very high specific gravity, 1076 the first day and 1052 the second. These figures were much higher than any obtained throughout the entire series of experiments, and although no exact metabolism experiments were made, as the case was of too short duration and the conditions too exceptional to make it of value, the rate of metabolism was evidently excessive and was unquestionably a great factor in the safety of the animal, for the next two dogs, in one instance on the same and in the other on a smaller amount of nitrogen per kilo, died of toxemia.

In trying to find a satisfactory explanation for this fact, viz., that this dog survived these injections, it was learned that Zachwegrwski[17] proved that in pregnant women there was antepartum nitrogen retention, and that postpartum there was a decided nitrogen loss, equilibrium not being established for four or five days, or even longer. He believed that the involution of the uterus caused the high nitrogen output accompanied by excessive nitrogen metabolism. It would certainly seem that this was the case, as the animal lost flesh out of proportion to the other animals, although it was on a higher percentage of nitrogen. So far as the pup is concerned, the method of hypodermic feeding of the mother failed to furnish the requisite amount of food, but as this was a very severe test for an artificial form of feeding, it is not surprising that it failed to meet these unusual demands.

TABLE 2.

	Date.	Weight kilos.	Volume Urine. c.c.	Urine. Sp. Gr.	Food.	Clinical Notes.
1.	July 29.....	5.21	215	1020	Regular	Well and lively.
2.	July 30.....	5.14	295	1012	Regular	
3.	July 31.....	5.19	135	1020	Regular	
4.*	Aug. 1.....	5.12	115	1076	0.4 gr. N. per k. in peptonized milk.	Dog vomited. Rather weak; gave birth to pup. Weight of pup 21 grams.
5.*	Aug. 2.....	5.03	295	1052	"	Dog still weak. Pup weight, 18 grams.
6.*	Aug. 3.....	4.90	365	1031	"	Dog still weak. Pup weight, 17 grams.
7.	Aug. 4.....	4.38	515	1011	Regular	Dog better. Pup weaker; 16 grams.
8.	Aug. 5.....	4.40	210	1020	Regular	Pup weaker; 15 grams. (Died next day.)

* Injection periods.

17. Ztschr. f. Biol., 1894, xxx, 405.

EXPERIMENT 4.—In order to see whether the peptonized milk would prove as toxic under what might be termed normal conditions, another dog was injected with the same amount of nitrogen per kilo, namely 0.4 gram, divided into two doses daily. After the first injection, the toxic symptoms of the peptone were very evident, for the dog looked sick and could not rise. It received only three injections, at twelve hour intervals, showing after each more and more evidence of toxemia and dying twelve hours after the third injection.

The autopsy showed marked subcutaneous edema on the flanks and under the belly; skin dark purple and ecchymotic. On section, this area of edema was found infiltrated with bloody, serous fluid. The organs were sent to the Cornell Pathologic Laboratory and the following report was received:

"*Liver.*—The whole section stains poorly. Many lobules show a marked degeneration as from a severe toxemia. The ability of the cell body and nucleus to take on basic stain has been lost, indicating changes in the direction of degeneration, if not necrosis. The vascular elements seem normal.

"*Kidney.*—Tubules were in a condition of cloudy swelling and granular degeneration. Glomeruli, interstitial tissue, blood vessels appear normal.

"*Heart and Spleen.*—Normal.

"*Intestines.*—Some congestion in spots; no hemorrhages."

EXPERIMENT 5.—The next trial to be recorded was with the peptonized skimmed milk, but peptonized only one hour and a half, as it was thought that possibly the length of the peptonization might make some difference in the degree of toxicity. Then instead of suddenly changing from all mouth feeding to all hypodermic feeding it was thought that it might be safer to make the change more gradually. The first day, three-quarters of the regular amount were given by mouth and one-quarter by hypodermic injection. The next day half mouth feeding and half hypodermic injection were resorted to, always on the basis of 0.3 gram nitrogen per kilo.

These injections caused some toxemia from the first, but it was not until the second day that the dog looked really ill, and on the morning of the third day he was found dead, apparently from the same form of toxemia as killed the preceding dog. The first day's injection represented 0.075 gram of nitrogen per kilo; the second day's, 0.15 gram of nitrogen per kilo.

The autopsy revealed local edema with serous bloody fluid. The examination of liver and kidneys could not be completed in time, but on gross examination presented only slight evidences of cloudy swelling.

Although the outlook for accomplishing artificial nutrition with anything like exactness by the use of milk seemed most unpromising, it was felt that with milk as the most readily obtainable food, easy of preparation and sterilization, it would be worth giving it a final trial in the hope that some immunity to the poisonous effects might be acquired by using very small amounts at a time and increasing very gradually, waiting for all symptoms to subside before repeating the treatment.

EXPERIMENT 6.—The milk was skimmed and peptonized as in the last experiment, for one and a half hours, then sterilized. A 50 per cent. glucose solution was also prepared, in order to see how this would act in connection with the milk, thus furnishing some extra heat units.

A lively dog was obtained, put on the laboratory fare, weighed daily, and allowed to reach practically a stationary weight, which it did on a diet of 0.61 gram of nitrogen per kilo, although on this diet it put on 0.4 to 0.5 gram of nitrogen. A period of thirteen days was consumed in the experimental feeding, previous to which the dog, as has already been stated, was at an almost constant weight, although the nitrogen balance showed the 0.4 to 0.5 gram plus per day.

The injections were begun with very small amounts, e. g., 0.098 gram of nitrogen per kilo, divided into two injections, and, as a rule, the amount was not increased for forty-eight hours. Including the two days on regular mouth feeding,

preceding the experiment, and on all the thirteen days during which hypodermic nutrition was successfully maintained, the nitrogen balance was determiend daily. While this always showed a minus balance, i. e., the dog was excreting more nitrogen than it received in the food injected, still, with each increase in the amount of food the minus balance grew steadily less until on the tenth and eleventh days it was only 0.5 gram of nitrogen, the body weight remaining almost constant on those days. The food was then reduced and the minus nitrogen balance again increased to —2.62 gram. On increasing the food, it again sank to —0.311 gram on the fourteenth day.

These injections were given precisely as the others, twice daily, twelve hours apart, under aseptic precautions, and the animal showed surprisingly little reaction to them. During the earlier days of the injections, when the amount of nitrogen injected was low and the dog, of course, losing weight, he was not so lively, but was not ill; as the quantity of nitrogen was increased to 0.33 gram per kilo his general well-being improved and he was bright, lively and apparently normal. Up to the point of receiving 0.22 gram of nitrogen per kilo, there was no biuret reaction in the urine, showing that the peptone was being utilized completely. After this, there was always a slight reaction, increasing somewhat as the percentage of nitrogen was increased, although the dog's apparent well-being was improved and he seemed normal.

At times there was a trace of albumin in the urine, but never more; at no time were there casts. The sugar injected varied from nearly 4 grams per kilo per day to a little less than 1 gram, and varying amounts could always be detected in the urine. The lactose from the milk injections alone gave a moderate reduction of the copper, but not a quick, strong reaction, as when the glucose was injected. No accurate estimations of the amount of excreted sugar were made.

The dog's temperature at the beginning of the experiment was 103° F. (somewhat above normal), and never rose over 103.2° F. during the entire period of thirteen days. After the first two days, the dog was never thirsty and refused water during the last eleven days; it received more water by the injections than it really needed.

After the twenty-sixth (the last) injection on the thirteenth day of this experiment, the dog played about, ran to his cage wagging his tail, showing a very nearly normal physical condition, except for the moderate loss in weight, 0.85 kilo. The loss of weight, which set in late in the experiment, probably shows that such a purely artificial form of nutrition can not be maintained indefinitely (Table 3).

SUMMARY.

In offering a short review of these experiments, the results may be stated in a few words as follows:

1. By the ordinary method of rectal alimentation it is practically impossible to nourish patients properly or to maintain nitrogenous equilibrium. There are probably few, if any, exceptions to this rule.

2. The hypodermic use of meat peptones and alkali albuminates is not feasible for artificial nutrition on account of their great toxicity and tendency to cause local necrosis.

3. Skimmed milk, peptonized one and one-half to three hours, may prove fatal if given hypodermically.

4. It was found possible to furnish a dog with full nitrogenous requirements in the form of skimmed milk, peptonized one and one-half hours, and injected hypodermically in gradually increasing doses; when

TABLE 3.

Day.	Weigth in kilos.	Volume of urine in c.c.	Sp. Gr. of urine.	Chemical Examination of urine. Albumin.	Sugar.	Biuret reaction.	Total urinary N., grams.	Food volume in c.c.	Total food N in gms.	Feces in gms.	Total fecal N in gms.	Nitrogen (gms.) in food per kilo of body weight.	Total nitrogen balance.	Remarks.
1.	6.60	230	1012	0	0	0	3.174	Reg.	4.034	39	0.458	0.61	+0.404 N	
2	6.55	255	1014	0	0	0	3.136	Reg.	4.034	25	0.320	0.61	+0.568 N	
3	6.68	145	1043	Trace.	+	0	4.364	135	0.656	0	0.	0.098	—3.708 N	Dog a little depressed.
4	6.50	395	1016	0	+	0	3.179	135	0.656	0	0.	0.1	—2.523 N	Dog better; lively.
5	6.31	220	1024	0	+	0	2.083	135	0.656	7	0.247	0.103	—1.674 N	Dog practically normal.
6	6.35	105+	1051	0	+	0	1.710	150	0.762	*	0.111	0.12	—1.059 N	Some urine contained feces, estimated as "liquid."
7	6.33	190+	1040	Trace.	+	0	2.622	150	0.762	*	0.287	0.12	—2.147 N	Some urine contained feces, estimated as "liquid."
8	6.30	210+	1040	Slight trace.	+	+	2.772	275	1.397	*	0.144	0.221	—1.524 N	Some urine contained feces, estimated as "liquid." First day with + biuret reaction.
9	6.25	255	1033	"	+	+	2.470	275	1.397	0	0.	0.223	—1.073 N	Dog apparently keeps well; not thirsty.
10	6.30	250	1038	"	+	Faint.	2.292	373	2.100	0	0.313	0.333	—0.505 N	Very small minus balance.
11	6.31	260	1038	"	+	"	2.646	373	2.100	0	0.	0.332	—0.546 N	
12	6.10	335	1024	"	+	"	2..401	202	1.139	0	0.	0.186	—2.622 N	Dog continues all right.
13	5.95	240	1033	"	+	"	2.299	205	1.150	6	0.394	0.193	—1.543 N	
14	6.00	215	1049	"	+	"	2.401	373	2.092	0	0.	0.348	—0.311 N	Smallest minus nitrogeous balance.
15	5.75	415+	1033	"	+	"	3.577	373	2.162	0	0.	0.337	—1.640 N	Dog lively and well; trotted back to cage.

* Liquid.

on the larger amounts of food the weight remained almost stationary, the nitrogenous balance showed only 0.3 to 0.5 gram loss, the dog being apparently physically in good condition.

5. For ordinary use, although successfully carried out in this instance, milk peptone when injected hypodermically must be considered dangerous, and until some method for avoiding the greater part of the natural toxicity of the product can be found, should not be used for nutritive purposes in man.

Since nutrition may be thus artificially carried out in dogs, it does not seem improbable that some modification of the method may be found that would be suitable for man, particularly as the minimum human nitrogen requirements are, per kilo, less than one-half that of the dog.

Addenda.—A subsequent attempt was made to nourish a dog on milk to which extract of pancreas had been added at the time of injection in the hope that the process of peptonization would take place slowly in the tissues, thus reducing the tendency to toxic effects from large amounts of peptone. The experiment, however, was a failure, as the material caused wide local necrosis and made the dog exceedingly ill. It was then thought that possibly a dog might be immunized against this form of peptone, that serum from this animal might prove effectual in protecting another. The attempt was made, but, although the dog which it was attempted to immunize showed a lessening reaction to the poisonous effects of the peptone, it never became immune. This, it was found, coincided with the experience of Friedman and Isaacs.[18]

My hearty thanks are due to the attending and house staff of the Presbyterian Hospital for the clinical material and to Prof. Wm. T. Gies, of the Department of Biologic Chemistry of Columbia University at the College of Physicians and Surgeons, for many helpful suggestions and valuable advice in connection with the metabolism experiments as they were carried out under his supervision.

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18. Zeitsch. f. Exp. Thera. Path., 1908.

THE RELATION OF IODIN TO THE STRUCTURE OF THE THYROID GLAND.

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INTRODUCTION.

The analyses and experiments embodied in this paper comprise the second stage of the work on the nature of goiter, viz.: the relation of iodin to the structure of the thyroid gland.

In previous papers one of us[1] discussed the structure of the thyroid in its various phases in the attempt to formulate basic anatomic types to which the individual glands could be referred. It was found that the various types of changes are quite easily separated into four natural groups, viz.:

(1) Normal glands.

(2) Glandular hyperplasias, all degrees (parenchymatous hypertrophies).

(3) Colloid glands, goiter (all degrees).

(4) Complications supervening in any of the three preceding groups.

It has also been pointed out[2] that the anatomic changes observed in developing goiters are of such nature, and occur under such peculiar conditions, and can be controlled by such particular procedures, that we are forced to conclude that they are physiologic reactions to some deficiency, or compensatory hyperplasias.

Among the factors which might be connected with this deficiency, iodin was rendered most prominent by the observations of Halsted[3] on compensatory hypertrophy, by the discovery of Baumann[4] of the normal presence of iodin in the thyroid and by the vast accumulation of clinical and experimental evidence of the specific therapeutic effect of iodin in

1. Cleveland Med. Jour., 1907, vi, p. 45; also Johns Hopkins Hosp. Bull., 1907, xviii, 359.

2. Jour. Infect. Dis., Chicago, 1907, iv, 417; also Cleveland Med. Jour., 1908, vii, 105.

3. Halsted, W. S., Johns Hopkins Hosp. Rep., 1896, i, 373; also Med. Rec., N. Y., 1888, xxxiv, 368.

4. Ztschr. f. physiol. Chem., 1896, xxi, 319.

the hyperplasic or parenchymatous glands. We were, therefore, led to investigate further the relation of iodin to the gland structure. This work, so ably begun by Baumann[5] and others, undoubtedly lost much of its real worth by their attempts to apply the discoveries to analogous conditions in the human being before the difficulties and complicating conditions were fully recognized. Moreover, as the discovery of iodin came at the time when the chemistry of thyroid opotherapy was attracting the attention of other physiologic chemists who were more particularly interested in the organic constituents of thyroid proteids, the views of the above-mentioned investigators (Baumann, Oswald,[6] Roos[7]) as to the relation and importance of iodin in the proteid molecule met great opposition.[8]

R. Hutchinson[9] asserts that the activity of the thyroid is due to the two proteids of the colloid, but, after examining them in the light of Baumann's work, he found that both contain iodin, adding that one has only to realize the small amount of iodin (a few mgm.) to recognize that it can not play an active part. Concluding, he says: "The colloid matter then is the active substance—the part which iodin plays it plays by virtue of the form of combination in which it occurs in the colloid and not by virtue of its being iodin." In a second paper[10] he still considers iodin of secondary importance to the proteids in the therapeutic value of thyroid extract, and adds that if iodin in the colloid be increased ten times, as it is possible to do, it does not increase its activity.

To-day, however, one feature is generally agreed on, viz.: that the physiologic activity of the (colloid) thyreoglobulin is dependent on the amount of iodin contained in organic combination. Hunt[11] has recently arrived at similar conclusions in a novel way—that of testing the resistance of animals to a poison (acetonitrile) with and without the administration of thyreoglobulin.

In this work we have attempted to eliminate as many of the complicating, perplexing and uncertain factors as our present knowledge would permit, and to include all the factors which were open to observation and which at the time seemed to have a bearing on the structure or chem-

5. Ztschr. f. physiol. Chem., Strassb., 1896-7, xxii, 1; also Baumann and Roos, ibid, 1896, xxi, 480.

6. Ibid., 1897, xxiii, 265; also Inaug. Diss., Strassb., 1900.

7. Ibid., 1896, xxi, 19; also Virchow's Archiv., 1902, clxix, 444.

8. Notkin, Wien. med. Wchnschr., 1895, xlv, S. 824; 872; also Fränkel, S., Wien. klin. Wchnschr., 1895, viii, 842; also Med. Record, N. Y., 1896, xlix, 37.

9. Jour. Physiol., 1896, xx, 474.

10. Jour. Physiol., 1898, xxiii, 178.

11. The Journal A. M. A., 1907, xlix, 1323.

istry of the gland. With this idea in view, we chose to use the dog and have appended the full table of analysis, the special features of which will be pointed out under their appropriate headings.

The general views as to the etiology of goiter may be divided into two groups: (1) that it is due to an infecting agent (miasm) and (2) that it is the manifestation of a nutritional disturbance. The former had its period of greatest development parallel with the early period of bacteriology (1850-1885). Virchow, Hirsch and, in particular, Ewald have supported this view.

The latter view, that it is a nutritional disturbance, has received its greatest support from experimental investigations. The experiments, accidental, as it were, of the elder Kocher, and Reverdin,[12] of the total removal of the gland in man, were probably the most suggestive in the early period. The work of Munk[13] on the importance of the thyroid gland to the animal, pointing to conclusions which were so contradictory to the prevailing views[14], stimulated Halsted,[3] in the early days of aseptic surgery, to repeat them. Halsted's fundamental experiments and observations, followed by those of Horsley[15] and Edmunds,[16] have established several important general biologic facts, chief among which are: (1) that the gland is essential to normal body economy; (2) that partial removal is followed by compensatory hyperplasia of the remaining portion; (3) that myxedematous conditions follow the total removal of the thyroid gland alone, and (4) that it is possible to produce experimentally congenital (goiter) hyperplasia of the thyroid.

The introduction of thyroid feeding into the treatment of myxedema and later into that of goiter, in general, was particularly associated with the names of Murray[17] and Mackenzie[18] in England and Bruns[19] in Germany. Advances in our knowledge of the chemistry of the gland followed quickly on the discovery of its therapeutic merits and are in particular associated with Hutchinson,[9] Fränkel,[8] Baumann,[5] Oswald[6] and Roos.[7]

The results of all the investigations included in the above summary have tended to show (1) that the thyroid gland is an organ essential to

12. Quoted in report of the committee on myxedema, Trans. Clin. Soc., Lond., 1888, No. 21.
13. Sitzungsber. d. k.-preuss. Akad. d. Wissensch. zu Berlin, 1887.
14. Schiff, Arch. f. exp. Path. u. Pharmakol., 1884, xviii, 25.
15. Brit. Med. Jour., Lond., 1895, i, 111, 211; also Internat. Beitr. z. Wissensch. Med., 1891, i, 369.
16. Jour. Path. and Bacteriol., Lond., 1894-6, iii, 488.
17. Lancet, Lond., 1893, i, 1130.
18. Ibid., 123.
19. Beitr. z. klin. Chir., 1894, xii, 847.

the normal metabolic activities of the animal; (2) that it probably has a definite secretion; (3) that iodin is an essential constituent of this secretion, and (4) that the various anatomic changes occurring in the gland are results of or reactions against general nutritional disturbances rather than specifically thyroid in origin.

ANATOMIC CONSIDERATIONS.

The trite phrase, that "our knowledge of structure must precede our knowledge of function," seems particularly applicable to the study of the thyroid. Indeed, in our experience, the thyroid gland offers one of the most striking examples yet encountered of the relationship between variations in physiologic activity and in anatomic structure. In this work, a classification of the thyroid changes that is at once simple of application, well defined, and as free from vagueness as possible is absolutely essential. The present state of our knowledge offers no condition or factor, other than structure, that is sufficiently constant or uniform to allow of its use as a basis of classification. By examining large numbers of thyroids, it has been found possible to differentiate types to which the various grades and stages of the changes can be made to conform. Thus, by making as few subdivisions of these pure types as is possible the existing confusion in nomenclature may be obviated to a large extent. We also think that the anatomic standard of classification in experimental work on the thyroid will permit comparisons with other observers' work which, at present, is not possible. Such a classification will allow us to refer all phases of the subject under investigation to a fairly constant anatomic base-line and render possible an analytic study of these phases.

The material for this work consists of the thyroid glands of a series of over one hundred dogs taken without discrimination as to weight, age, sex or breed from the several department laboratories. Care was taken, however, to get the thyroids as soon as possible after the dogs were brought from the street in order that the findings might with justice be taken as an index of the normal street condition. As factors which might conceivably affect the condition of the thyroid, we observed the age, sex, breed, weight and state of nutrition. Records were made of all these conditions, though as regards age and breed gross errors are probable. The thyroid glands were weighed fresh; brief descriptions of color, consistency and visible colloid were noted; a small piece for microscopic

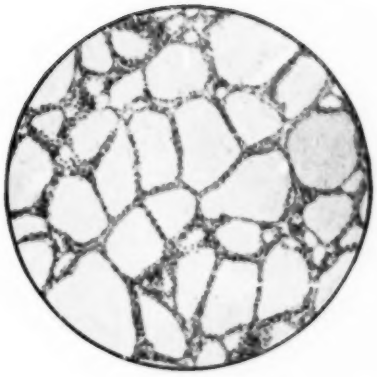

Fig. 1.—Normal thyroid, dog.

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Illustrating Article by David Marine, M.D.
and W. W. Williams, M.D.

examination was then removed, and the gland reweighed and referred to Dr. Williams for iodin determination.[20]

As a result of an extensive experience with the anatomic appearances of the dog's thyroid, we have found that, while in general one can make fairly accurate determinations as to the type and even the grade of change from the gross appearance, there is always the chance for error; e. g., small glands may show quite marked hyperplastic changes, though, as a rule, the enlargement is proportional to the degree of glandular hyperplasia. Likewise, while the color and consistency and blood vessels, in general, conform to the glandular changes, reliance on them may be a source of error, as pointed out by Halsted.[3] The microscopic appearance, therefore, has been our sole final guide to the group or subgroup to which each gland was referred.

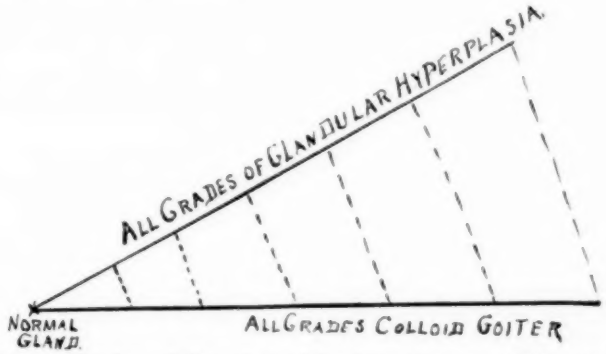


Fig. 2.—Showing relation of glandular hyperplasia to colloid goiter.

Barring complications, the three natural groups are, as previously stated: (1) normal glands, (2) colloid glands, (3) hyperplastic glands. Subgroups have been made only of Group 3—the glandular hyperplasias. It was further found necessary to make double reference to several of the glands, as "*normal X early*," "*colloid X early*," "*early X moderate*," or "*moderate X marked*." These will be considered as intermediate groups. Brief anatomic descriptions of the groups and subgroups follow:

Group 1. *Normal Gland.*—The normal gland is similar, as to all its essential anatomic features, in all mammals examined. In herbivora, as a rule, the gland has coarser lobulations and more stroma. In the

20. The iodin determinations were made quite independently of the histologic work, and the anatomic groupings were made independently of the iodin determinations.

dog, the normal gland has a thin gray translucent capsule. The gland tissue is firm and of a yellow translucent color, due to the abundance of syrupy colloid. The blood and lymph vessels are very small. Microscopically, the acini are rounded, fairly regular spaces, lined by a single layer of flat cubical epithelium. The epithelial nuclei are small, flattened and darkly staining. The colloid is quite uniform and homogeneous in its staining reaction and sharply abuts on the lining epithelium. The stroma is very scanty. All glands conforming to this description were considered normal (Fig. 1). Glands to which there are double references are not included in the analytical tables. In our series there were but three[21] glands (A-38-87-98) which conformed to this rigorous standard—two from females and one from a male. All three dogs were in a fair state of general nutrition. Regarding age and breed there is nothing significant.

Group 2. *Colloid Gland.*—The colloid gland (goiter) in its uncomplicated form may be considered as an exaggeration of all the normal gland structures. Since it has been shown definitely by one of us that practically, if not quite all, colloid glands (goiters) have been preceded by a hyperplastic stage and are to be considered as the reverted and quiescent or as nearly the normal state as a gland can ever become which has once been the seat of a glandular hyperplasia, it then follows that we have to deal with all grades of the colloid condition, depending on the degree of hyperplasia preceding it. We think it necessary to consider all thyroids as colloid glands if they show any microscopic evidence of having had any grade of glandular hyperplasia preceding, no matter if their size, color, consistency and general appearance at the time of obtaining coincide with those of a normal gland. This view is shown more clearly in Figure 2.

To take, then, a moderate example of a colloid gland, the anatomic findings are as follows: The gland is symmetrically enlarged and very firm, the capsule is somewhat thickened and opaque, while the acini are large, well defined and filled with clear yellowish colloid. The tissue is translucent and not vascular. Microscopically, the arteries show an obliterating endarteritis similar to that occurring in the uterine or thymic vessels during involution. The colloid stains uniformly and densely and abuts sharply on the epithelium. The acinar epithelium is

21. The findings of but three absolutely normal glands out of the 113 specimens is due to the very rigid standard of normal adopted, viz., the seacoast type. Many ordinarily called normal were classified in the intermediate groups, i. e., under the double reference "normal x early" or "normal x colloid." These finer distinctions are only of value for scientific accuracy.

flat-cubical and arranged in a single layer. The nuclei are flattened, small and darkly staining. Depending on the degree of preceding glandular hyperplasia and on the duration of the colloid stage, there are more or less numerous sprigs of acinar epithelium jutting into the lumina of the acini, which are the remnants of the invaginations and plications of the epithelium during the hyperplastic stage. As may be inferred from Figure 2, there are stages in the process of reversion when it would be impossible to decide whether the histologic changes are to be considered progressive or reversive; hence, there is some difficulty of determining even histologically whether a given specimen ought to be considered with the colloids or with the hyperplasias.

Only glands conforming to the above anatomic description were considered as colloid in the analytical tables—the glands to which double references were made being classed in the intermediate group. There were eight cases (A-13, 25, 43, 48, 78, 80, 86, 90)—two females and six males. Relative to the state of nutrition, five were good or above and three were fair. It is significant that all cases occurred in middle-aged or old dogs. Our general impression is that in the dog sex has little or no influence on the structure of the thyroid (Fig. 3).

GROUP 3. *Glandular Hyperplasias.*—This group includes the most important thyroid changes, and it is with these changes in particular that this paper has to deal. Their greatest importance lies in the fact that they represent the primary changes[22] in the formation of all true goiters (functional hyperplasias), and hence must receive primary consideration in all inquiries into the nature of goiter. As pointed out above, there are all grades of these changes, from the normal gland to the most marked hyperplastic stage where there is scarcely any resemblance to thyroid at all. For this reason we have arbitrarily made three subgroups for analytical purposes. These groups are:

SUBGROUP 1. *Early Glandular Hyperplasias.*—This division comprises those glands which are but slightly removed from the normal. Several of the glands closely related to this subgroup are connected by double reference with the normal glands and included in the intermediate group of "normal X early." This is due to the fact that the changes are so slight that with fairness they must be considered doubly or not at all. These glands are not included in the primary analytical tables.

A typical example may be described briefly as follows: The gross appearance is nearly normal. The gland may perhaps be slightly en-

22. Virchow, Die Krankhaften Geschülste, iii, 4 et seq.

larged or of a pinkish hue if compared with a normal gland. The tissue is firm to the touch and on section colloid is visible. Microscopically, the acini are small, generally circular and regular. The colloid appears normal or nearly so as to staining reaction, but after some experience one can distinguish a slight vacuolization or at least a lessened staining intensity. The epithelium is regular and of a high cubical or low columnar type. There are here and there the very beginnings of invaginations and plications of the lining epithelium. The nuclei are slightly enlarged and darkly staining, but distinctly vesicular. There is no demonstrable increase in the stroma, but the vessels, particularly the finer ramifications, appear distinctly dilated. All glands conforming to this description are considered in this subgroup (Fig. 4). In our series there were nine cases—four females and five males (A- 39, 40, 57, 62, 65, 84, 88, 92, 103). All were considered to be in the middle period of life and in all the general nutrition was good. As to breed there is nothing of importance.

Subgroup 2. *Moderate Glandular Hyperplasias.*—This division likewise offers difficulties and opportunities for error when the attempt is made to bring into a single group. Hence many closely related glands are connected by double references with either colloids or early or marked glandular hyperplasias. The reason why some are connected by double reference with colloids is that occasionally one finds glands which appear to be reverting from a marked degree of hyperplasia, but at the time of taking were histologically much like moderate hyperplasias. Only undoubted cases were, however, included in the tables for chemical analysis.

Briefly, the anatomic appearances of a typical case are: The gland is moderately enlarged, the vessels are distinctly enlarged and somewhat tortuous, the capsule is thickened and the gland tissue is moderately soft and reddish in color. There may be visible colloid. Microscopically, the colloid is reduced, vacuolated, palely staining and granular, The acini are distorted by moderate ingrowths and plications of the epithelium. The acinar epithelium is high columnar in type, regular and arranged in a single layer. The nuclei are large, round, basal and vesicular. The stroma is slightly but diffusely increased and supports a rich network of dilated and enlarged blood vessels (Fig. 5). In our series there were nine cases (A-3, 6, 21, 34, 35, 60, 70, 76, 78)—eight males and one female. It is of interest to note that only three were considered in a good state of general nutrition. As to age and breed there is again nothing of significance.

Fig. 3.—Colloid gland (goiter), dog.

Fig. 4.—Early glandular hyperplasia, dog.

Subgroup 3. *Marked Glandular Hyperplasias.*—Glands in this stage of hyperplasia are more easily referred to an arbitrary subgroup for the reason that only the subgroup of moderate hyperplasias is to be differentiated, but here, too, an intermediate group is necessary.

The anatomic appearances of a typical example are as follows: The gland generally is considerably enlarged, but, as pointed out above, there may be very marked histologic changes without corresponding changes in the gross appearance. The capsule is thick and the vessels are much enlarged and tortuous. The lymphatic trunks are large, and, if exposed during life, are distended with a clear lymph-like fluid. On section the tissue is very vascular. It has a fleshy, opaque, gray-red appearance and a finely granular cut surface. There is no visible colloid. Microscopically, the stainable colloid is greatly reduced or absent, there being in its place only a small amount of pink staining granular material. The acini show extensive papillomatous ingrowths and plications of their lining epithelium, more or less effacing the acinar lumina. The epithelium is high columnar in type and arranged in a single layer. The epithelial nuclei are large, pale, round and basal. The cytoplasm is quite granular. The stroma is diffusely increased and is richly supplied with blood and lymph channels. There are also occasional collections of lymphoid cells in the stroma (Fig. 6). Only specimens conforming to the above description are considered in the analytical tables of this subgroup. In our series there are eighteen cases (A-2, 4, 10, 14, 15, 19, 23, 24, 28, 29, 41, 46, 47, 54, 67, 79, 99, 102)—ten males and eight females. As regards the state of nutrition, eight were classed as fair and ten as good. Relative to age the majority were young.

General Considerations of Sex, Age, Breed and State of Nutrition as Affecting the Structure of the Thyroid.

(a) *Sex.*—In this series there were forty-five females and fifty-eight males. (The remaining ten in the table were selected.) Sex does not appear to be a factor of noteworthy importance in the occurrence of thyroid changes in the dog; at least in the 103 cases included in this study no such relationship could be made out. From an experience with over 600 dogs our general impression is the same. This is quite different from the condition which obtains in man, and suggests that sexual states modify but slightly the activity of the thyroid of dogs as compared with man. Pregnancy, however, does induce hyperplasic changes similar to those occurring in man.

(b) *Age.*—Age is of more importance than is indicated in this series

for the reason that practically all the cases were from adult animals. From a series of over 600 dogs we have found that puppies are much more frequently affected, and, as a rule, the hyperplasia begins before the sixth month of extrauterine life. Authors generally are agreed that youth is the most important period in the human hyperplasias as well. Age is also a notable factor in the chemistry, as will be pointed out later. Age does not bear any important relation to normal glands. Colloid glands, however, are commoner in middle aged or old dogs without relation to sex. This conforms with the view that colloid glands (goiters) are reversions from hyperplasias.

(c) *Breed* in our laboratory class of dogs is an uncertain factor. Some authors think that, clinically, goiter is commoner in spaniels, but in our experience (using the histologic standard) we are unable to ascribe any importance to breed.

(d) The state of *nutrition* seems to be a factor of considerable importance both as a cause for and as an effect of the thyroid changes. All dogs with normal, colloid or early hyperplastic glands were found to be in a condition above fair,[22] while in the moderate and marked hyperplasias thirteen out of twenty-six were below this standard. Since fat is an apparent rather than a real index of nutrition, and since it is highly probable that goiter is a nutritional disturbance, it is also probable that great exceptions or variations will be noticed by the use of such a crude index, which, however, might be rationally explained if our knowledge of nutrition were more thorough.

CHEMICAL CONSIDERATIONS; IODIN DETERMINATIONS.

(1) The *method* used in all the determinations of the amount of iodin present in the glands and tissues investigated was based on that originally described by Rabourdin[23] and extensively used by Baumann and Roos[24] in their thyroid work. The basis of the method is the fact that the amount of iodin dissolved in chloroform can be determined by the depth of the pinkish tinge which it gives to the solution. Briefly, the method consisted in incinerating the tissue in a silver dish in the presence of an alkali and potassium nitrate, and after dissolving in water the iodin was liberated by acidulating with sulphuric acid; it was then shaken out with chloroform. In another flask a known amount of iodin was added to chloroform until the tint was the same as that in the first flask.

22. We have used in all of our work the following terms, poor, moderate, fair, good, excellent, using as the index the visible fat noted at autopsy.

23. Lieb. Ann., 76, S. 375.

24. Ztschr. f. physiol. Chem., Strassb., 1896, xxi, 481.

Baumann[25] asserted that the method was not very accurate, and Oswald[26] found that amounts under 0.3 mg. of iodin could not be detected when the material was incinerated in a silver dish by this method. He substituted a nickel dish and found that from 0.1 mg. of iodin he could recover 0.08 mg., while with larger amounts the percentage of loss was much less. These workers also found that the iodin-chloroform solution soon faded, and if the determination was not made quickly the result was very inaccurate and unsatisfactory. To overcome this disadvantage Anten[27] used carbon disulphid instead of chloroform, and found that the color was much more permanent.

Our method embraces these modifications, and was carried out as follows:

The fresh tissue is weighed and is then cut into small pieces and dried to an approximately constant weight at 110 C. The dried gland is powdered and 1 gm. is taken for the iodin determination.

In a nickel evaporating dish 2 gm. of pure potassium hydroxid are dissolved in 5-10 c.c. of distilled water, and to this the 1 gm. of powdered gland is added. This is slowly evaporated to dryness, then carbonized, and on the addition of potassium nitrate the mass is reduced to a clear flux, care being taken not to add an excess of the nitrate. After cooling, the flux is dissolved in 50 c.c. of distilled water and filtered. The filter is washed with distilled water until it no longer gives a precipitate with silver nitrate. To the filtrate is added 10 c.c. carbon disulphid, 3 c.c. of 10 per cent. sulphuric acid, and 2 c.c. concentrated sulphuric acid, saturated with nitrous acid. While adding the acids the flask is well shaken, and if iodin is present the carbon disulphid takes on a reddish-violet tinge.

Into another flask saturated sodium sulphate solution is poured until it is approximately equal in amount to the liquid in the first flask. To this is added 10 c.c. carbon disulphid, 3 c.c. of 10 per cent. sulphuric acid, and 2 c.c. concentrated sulphuric acid, saturated with nitrous acid. From a burette a potassium iodid solution containing 0.1538 mg. iodin per cubic centimeter (0.20 gm. exsiccated KI to 1 L. distilled water) is run in until the color of the carbon disulphid is the same as that in the other flask. Reading off the amount of potassium iodid solution used, it is a simple matter to determine the amount of iodin in the original solution.

25. Ztschr. f. physiol. Chem., 1896-7, xxii, 265.
26. Ztschr. f. physiol. Chem., Strassb., 1897, xxiii, 265.
27. Arch. f. exper. Path. u. Pharmakol., 1902, xlviii, 331.

The flasks used for the colorimetric method are similar to those described by Howald,[28] and have a capacity of 500 c.c. with the neck drawn out into a tube about 15 cm. long and 1.5 cm. in diameter and are glass stoppered.

Another method which was used as a control in fifteen determinations is that described by Fresenius.[29] The gland is treated exactly as has been described for the colorimetric method, and the liberated iodin is dissolved in carbon disulphid. This is then decolorized by adding from a burette a standardized solution of sodium thiosulphate, and the iodin determined by the amount of the thiosulphate solution used.

In comparing the results obtained by the two methods there occurred in one case a difference of 0.1 mg. of iodin, but, as a rule, the differences were well below this figure.

To determine whether preserved glands could be used for these determinations, parts of six glands were hardened in a 4 per cent. solution of formaldehyd in distilled water and then the iodin content was compared with that of a part of the gland treated in the usual manner. Three of the formaldehyd specimens had a slightly higher amount of iodin than the controls, but the difference between the average of those above and those below the mean was only 0.009 mg. iodin. It is, therefore, quite justifiable to use specimens preserved by formaldehyd.

(2) *Analysis of the Iodin Determinations.* Iodin determinations were made on 113 dogs' thyroids. The primary tables were made from the pure anatomic groups and subgroups, and hence include only the 67 cases there considered. This was done in the attempt to exclude all known conditions which might artificially modify the iodin content, and further, in order that the results might be taken to indicate the normal street condition. Many of the remaining 46 determinations will be utilized in the intermediate groups of Table 5 and in the analyses of the separate groups to show that the chemical conditions correspond with the anatomic relations. The remaining cases will be discussed under experimental observations.

(a) Beginning with Table 1 the following features are noted:

Excluding the colloid glands (goiters), it is found that the average amount of thyroid per kg. of body weight is practicallw the same (0.36 and 0.30 gm.) for the normals and early glandular hyperplasias, and that the moderate and marked hyperplasias show a progressive increase

28. Ztschr. f. physiol. Chem., 1897, xxiii, 212.
29. Traité d'analyse chemique, 6th ed., p. 406.

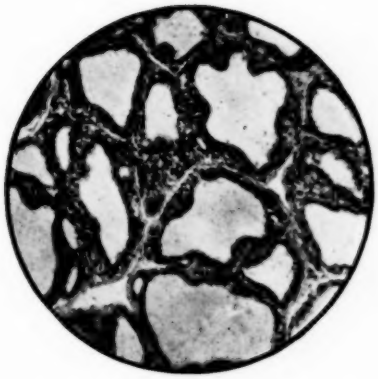


Fig. 5.—Moderate glandular hyperplasia, dog.

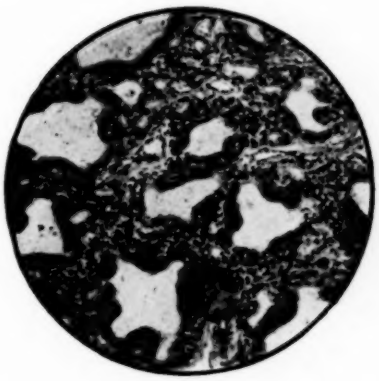


Fig. 6.—Marked glandular hyperplasia, dog.

TABLE I—Amount of Thyroid Compared with Body Weight.

Character of Gland.	Number.	Weight of Dog. Expressed in Kg.			Weight of Thyroid Expressed in gm.			Dried Thyroid Expressed in gm.			Fresh Thyroid per Kg. Body Weight. Expressed in gm.			Percentage Water in Fresh Thyroid.		
		E.*	M.	A.	E.	M.	A.	E.	M.	A.	E.	M.	A.	E.	M.	A.
Normal.....	3	6.3 4.7	5.9	5.6	3.65 1.3	1.3	2.08	0.95 0.29	0.307	0.516	0.61 0.20	0.27	0.36	78 74	77	76
Colloid.....	8	13.6 5.4	9.1	9.1	20.45 1.25	7.32	8.54	5.57 0.115	1.49	2.13	3.19 0.21	0.73	1.07	91 68	73	76
Early.....	9	15. 5.	8.2	9.3	4.5 1.3	3.	2.76	1.184 0.22	0.65	0.643	0.45 0.15	0.30	0.30	83 72	74	77
Moderate.....	9	15.9 5.	8.2	8.56	22. 1.5	3.6	7.36	5.75 0.31	0.77	1.70	3.20 0.21	0.65	0.92	85 73	78	77
Marked.....	18	34.5 2.5	7.2	10.	77.9 3.2	7.1	16.45	18.2 0.44	1.36	3.59	13.2 0.23	1.135	2.34	88 69	80	80

* E = extremes; M = mean; A = average.

(0.92 and 2.34 gm. respectively). The colloids are intermediate between the moderate and marked hyperplasias (1.07 gm). It is also interesting to note, as pointed out by Oswald,[30] that the hyperplasias are reduced more in weight during the process of drying, i. e., contain a larger percentage of water than either the normals or colloids.

TABLE 2.—Iodin Content of Thyroid; expressed in Milligrams.

Character of Gland.	No.	Total Iodin.			Per Kilogram of Body Weight.			Per Gram of Fresh Thyroid.			Per Gram of Dried Thyroid.		
		E	M	A	E	M	A	E	M	A	E	M	A
		1.891			0.32			1.064			4.772		
Normal. . .	3		1.384	1.419		0.294	0.256		0.757	0.777		3.205	3.322
		0.984			0.156			0.512			1.990		
		6.675			1 236			1.039			3.608		
Colloid. . . .	8		3.013	3.232		0.359	0.402		0.406	0.450		1.816	1.985
		0.415			0.069			0.132			0.846		
		0.892			0.084			0.235			1.028		
Early	9		0.400	0.443		0.033	0.044		0.133	0.139		0.654	0.625
		0.107			0.012			0 063			0.243		
		1.679			0.173			0.137			0.854		
Moderate . .	9		0.399	0.539		0.061	0.069		0.076	0.078		0.345	0.368
		0.061			0.006			0.026			0.101		
		1.430			0.242			0.123			0.640		
Marked. . .	18		0.092	0.293		0.020	0.039		0.014	0.023		0.073	0.114
		0.013			0.002			0.002			0.008		

(b) In Table 2 the following points are brought out:

That the colloid glands (goiters) contain the most iodin—over twice as much as the normal glands—and that the hyperplasias show a decreasing amount, being least in the marked glandular hyperplasias, in spite of the fact that these glands show a progressive increase in weight, as shown in Table 1. As also noted in Table 1, the colloid glands (goiters) average more than four times the weight of the normal glands, and this accounts for the large amount of total iodin. But considering the amount of iodin per gm. of fresh thyroid, it is seen that the normal glands contain about 0.8 mg. per gm. and that there is a progressive de-

30. Ztschr. f. physiol. Chem., 1897, xxiii, 272.

crease reaching the minimum of 0.023 mg. per gm. in the marked hyperplasias.

There being but three normal glands included in this series, it is not justifiable to consider the base line as very definitely established, but the extremes being reasonably close together, it is probably not very incorrect.

Among the colloid glands (goiters) great variations are noted in the iodin content, due possibly to the strict histologic basis of classification[31]

TABLE 3.—Percentage of Iodin.

Character of Gland.	No.	Per Body Weight.[1]			Per Fresh Thyroid.[2]			Per Dried Thyroid.[2]		
		E	M	A	E	M	A	E	M	A
		32			106			477		
Normal	3		29	25		76	77		317	331
		15			51			199		
		123			104			332		
Colloid	8		38	41		41	46		181	195
		7			13			84		
		8			23			102		
Early	9		3	4		13	14		65	62
		1			6			24		
		14			14			85		
Moderate	9		6	6		8	8		34	37
		0.7			3			10		
		24			12			64		
Marked	18		1.5	3.8		1	2		8.5	11
		0.2			0.2			0.8		

1 = mgm. per kg. 2 = mgm. per gm.

(being irrespective of the size of the gland), and also to the possibility of the gland having just begun to undergo secondary hyperplasias (too early to be detected by any microscopic difference), in which case the iodin content is relatively low.

31. That is, all glands are considered as colloids if there is any histologic evidence that they had ever undergone any degree of hyperplasia no matter how slight. This classification would, therefore, be only of scientific value for the purpose of preserving uniformity.

(c) The percentage of iodin, compared with the body weight, is about 15 per cent. greater in the colloid than in the normal glands, whereas the hyperplasias contain about 20 per cent. less than the normal glands. Here, also, there is a tendency toward a progressive diminution of iodin depending on the degree of hyperplasia. A notable exception, however, is the group of moderate glandular hyperplasias, which contain a larger percentage of iodin than the early hyperplasias, and, as before stated, this can probably be accounted for by the difficulty of determining whether a gland is reverting to a colloid—when the iodin content is higher or developing a hyperplasia from a colloid base, in which case the iodin content is lower.

The percentage of iodin per gm. of fresh thyroid shows a progressive decrease from the normal glands through the colloids to the marked glandular hyperplasias.

Comparing the percentage of iodin in the normal glands with that in the colloid glands, it is seen that in the normal glands it is less per kg. of body weight and therefore absolutely less, while per gm. of thyroid it is much greater, showing that the colloid glands possess absolutely more iodin, although they are relatively poorer.

(d) Table 4 takes into account the extremes noted in Table 2 and is so arranged that each group is divided into those above and those below the average of the preceding group. As is to be expected, partly from reasons already given, the colloid glands (goiters) show the greatest extremes, but by comparing the iodin content of the glands above with that of the glands below the average content of the group preceding (normal), it is found that 75 per cent. have a greater absolute amount of iodin, but when the iodin is calculated per gm. of fresh thyroid, 89 per cent. fall below the average preceding (normal) content. All the early hyperplasias show a decrease below the colloid averages in total iodin and in iodin per gm. of fresh thyroid.

Allusion has been made to the difficulties encountered in grouping the moderate hyperplasias. The average of the total iodin in the nine cases of moderate hyperplasia shows 56 per cent. to be below the average for the preceding (early hyperplasias) group and all to be below when the iodin is calculated per gm. of fresh thyroid. Among the marked hyperplasias 78 per cent. are below the average total iodin content of the moderate hyperplasias and 95 per cent. below when calculated per gm. of fresh thyroid.

Considering all the groups, the extremes bear out the conclusions deduced from the means (Table 2), namely: that there is a progressive decrease in the iodin content per gm. of fresh thyroid from the normal glands through the hyperplasias.

TABLE 4.—Analysis of Extremes in Iodin Content noted in Table 2.

Character of Gland.	No.		Total Iodin.			Iodin per Kg. of Body Weight.			Iodin per Gm. of Fresh Thyroid.			Iodin per Gm. of Dried Thyroid.		
			E	M	A	E	M	A	E	M	A	E	M	A
Normal. . .	3		1.891 0.984	1.384	1.419	0.320 0.156	0.204	0.256	1.064 0.512	0.757	0.777	4.772 1.990	3.205	3.322
Colloid . .	8	Above preceding Average.	6* 6.675	4.000	4.059	5 1.236	0.397	0.585	1	1.039		1	3.608	
			1.753			0.351								
		Below...	2* 1.091	—	0.753	3 0.128	0.093	0.097	7 0.565	0.389	0.377	7 3.261	1.599	1.755
			0.415			0.069			0.132			0.846		
Early. . . .	9	Above...		0			0			0			0	
			9 0.892			9 0.684			9 0.235			9 1.028		
		Below...		0.400	0.443		0.038	0.044		0.133	0.139		0.654	0.625
			0.107			0.012			0.063			0.243		
Moderate. .	9	Above...	4 1.679	0.796	0.969	5 0.173	0.115	0.111		0		1	0.854	
			0.608			0.061								
		Below...	5 0.399	0.123	0.195	4 0.039	0.013	0.018	9 0.137	0.076	0.078	8 0.519	0.318	0.308
			0.061			0.006			0.026			0.101		
Marked . .	18	Above...	4 1.430	0.818	0.920	3 0.242	0.135	0.156	1	0.123		1	0.640	
			0.615			0.091								
		Below...	14 0.473	0.080	0.114	15 0.035	0.014	0.016	17 0.042	0.014	0.016	17 0.184	0.069	0.083
			0.013			0.002			0.002			0.008		

* Figures indicate the number of glands.

TABLE 5.—Average Iodin Content of Pure and Intermediate Groups, Arranged in Anatomic Order.

Character of Glands.	No. of Cases.	Iodin per kg. of Body Weight.	Iodin per gm. of Fresh Thyroid.	Iodin per gm. of Dried Thyroid.	Fresh Thyroid per kg. of Body Weight.
Normals (pure)	3	0.256	0.777	3.322	0.27
Normals X colloids (intermediate)	1	0.218	0.480	2.480	0.46
Normals X early (intermediate)	7	0.054	0.173	0.881	0.27
Colloids (pure)	8	0.402	0.459	1.985	0.73
Colloid X early (intermediate)	4	0.181	0.217	0.914	0.79
Early (pure)	9	0.044	0.139	0.624	0.30
Early X moderate (intermediate	1	?	0.082	0.282	?
Moderate (pure)	9	0.069	0.078	0.368	0.65
Moderate X marked (intermediate)	9	0.096	0.055	0.283	1.52
Marked (pure)		0.039	0.023	0.114	1.14

(e) This table includes, besides the cases belonging to the pure histologic groups, those which are intermediate or which possess characters common to two groups, and excludes all cases which are complicated with neoplasm, hemorrhage, cystic changes, etc., and those operated upon or having received iodin in the laboratory or elsewhere.

It is compiled from averages only, and shows that the intermediate groups have iodin contents which fall between the iodin contents of the groups to which they are connected by double references. This table accentuates the fact brought out in Table 2 that the iodin per gm. of thyroid shows a progressive decrease from the normal glands through colloids to the hyperplasias, including the intermediate cases with double references.

(f) *Analyses of the individual cases of separate groups.* It will be noted that the extremes in the iodin content within the separate groups show such marked differences that it seemed unsafe to base conclusions solely on the averages. We compared, therefore, the iodin content with the anatomic changes of the individual members of each group.

Normal Glands.—The normal glands do not show very marked extremes, but as but three glands were considered, it is possible that a larger number might have shown greater variations. It is of interest, however, to note that in these cases the amount of iodin per gm. of thyroid varied inversely with the amount of iodin per kg. of body weight. An explanation of this fact might be that while the normal glands tend

to a more or less constant amount of iodin per gm. of thyroid, this constancy is not absolute, and when there is a greater quantity of thyroid tissue in one case the percentage of iodin will be less than in another case having less thyroid tissue.

As will be shown in the other groups, there seem to be comparatively wide limits in the iodin content between which there are no demonstrable histologic changes. On the other hand, there seems to be a fairly definite minimal amount of iodin per gm. of thyroid necessary for the maintenance of the normal histological appearance of the epithelium. If the iodin content falls below this minimal amount, hyperplastic changes in the gland follow. This minimal iodin content per gm. of thyroid is practically the same for the colloid and the normal glands as is shown in Table 5. In this table it is seen that hyperplastic changes have started when the iodin content falls below 0.173 mg. per gm. of fresh thyroid in the normal glands and to 0.217 mg. in the colloid glands.

Colloid Glands (*goiters*).—In the glands comprising this group there is, in general, an increase in the amount of iodin per gm. of thyroid associated with flattening of the epithelial cells and a decrease in the iodin in those glands having more cubical epithelial cells. As regards the relation between the amount of thyroid per kg. of body weight and the histologic changes—the smaller glands show evidence of epithelial activity (hyperplasia), while the larger glands show no such activity (cells very flat cubical).

Examining the cases further, it is found that six of the eight glands show that the increase in the amount of iodin per gm. of thyroid is coincident with a decrease in the amount of thyroid per kg. of body weight; in other words, the percentage of iodin is inversely proportional to the amount of thyroid, but since the amount of thyroid is very greatly increased, the total amount of iodin is also much increased, notwithstanding the fact that the colloid is relatively poorer in iodin than is normal colloid. This inverse proportion of iodin to the amount of thyroid agrees with that already noted in the normal glands, and our explanation is the same.

We have already pointed out that the colloid gland is as nearly normal as a gland can become after once having undergone a hyperplastic change, and it is of particular interest that the chemical findings should sustain this opinion which was based primarily on the histology, but which is now supplemented by the biologic facts that partial removal of colloids is followed by compensatory hyperplasia of the remaining por-

tion, and also, as shown by Baumann[32] for the normal glands, that compensatory hypertrophy occurs when iodin is restricted in the diet.

Oswald[33] has shown that in man and calves the iodin content in general varies with the amount of colloid in the gland, and also that in colloid goiters the percentage of iodin is decreased as compared with normal colloid. Our results with dog's colloid goiters agree with his findings.

Analyzing the glands still further, it is seen that, notwithstanding the comparatively low percentage of iodin in the colloid glands, the amount is always larger than that in colloids beginning to undergo hyperplasia. It seems probable that before a glandular hyperplasia can revert to a colloid, a necessary minimal amount of iodin must be present. Further, that reversion having once begun, the colloid accumulates more rapidly than iodin can be accumulated in the colloid (in the presence of a limited supply of iodin) without interfering with the physiologic requirements of the body at large, and, therefore, we have a colloid which is relatively poor in iodin as compared with normal colloid, although the absolute amount of iodin in the whole gland may be and is much greater than in a normal gland, and is, if our interpretation be correct, necessarily greater than the normal physiologic needs of the organism. But in the presence of a large excess of iodin the colloid of a reverting hyperplastic gland is capable of assimilating as much iodin as normal colloid. In other words, a certain amount of iodin is necessary before reversion can occur at all. If this supply of iodin be only slightly in excess of the physiologic needs, then the large amount of colloid which is formed will be relatively poor in iodin, although the total iodin in the gland may be and is actually greater than that present in a normal gland. If, on the other hand, the gland reverts in the presence of a larger excess of iodin, the colloid which is formed will be rich in iodin, approaching or equalling the iodin content of the colloid of normal glands.

"Colloid X Early" Glandular Hyperplasia.—This group shows that the amount of colloid in the gland decreases as the amount of iodin increases; that the colloid decreases as the gland becomes smaller, and that the iodin per gm. of fresh thyroid decreases as the gland becomes larger. These conclusions hold good for three out of four glands—the fourth gland was reverting from a marked hyperplasia, while the others were in the early stage of secondary hyperplasia engrafted on colloid bases.

32. Ztschr. f. physiol. Chem., 1896-7, xxii, 14.
33. Ztschr. f. physiol. Chem., 1897, xxiii, 265.

"Normal X Early" Glandular Hyperplasia.—In this group, roughly speaking, the amount of iodin per gm. of fresh thyroid decreases as the amount of thyroid per kg. of body weight increases. Moreover, the amount of colloid decreases as the amount of thyroid per kg. of body weight increases, and, finally, in two-thirds of the glands the amount of iodin decreases as the colloid decreases. Altogether the results are neither striking nor conclusive.

Early Glandular Hyperplasias.—The amount of iodin per gm. of fresh thyroid decreases as the amount of thyroid per kg. of body weight increases. There is no apparent relation between the amount of iodin and the amount of colloid present in the gland, nor does the degree of hyperplasia bear any marked relationship to any of the other factors. The amount of thyroid per kg. of body weight varies inversely with the amount of colloid in a fairly constant manner—the only striking exception—A-103—approaches histologically the next group.

Moderate Glandular Hyperplasias.—With the exception of three glands, the amount of iodin per gm. of fresh thyroid varies directly with the amount of thyroid per kg. of body weight. Two of the three exceptions have such an unusually large amount of thyroid per kg. of body weight that they suggest some other pathological changes. Roughly speaking, the amount of iodin increases as the amount of colloid increases. No relation seems to exist between the amount of colloid and the amount of thyroid per kg. of body weight. The epithelial differences are not sufficiently characteristic to permit drawing any conclusions.

"Moderate X Marked" Glandular Hyperplasia.—In seven out of the nine glands the iodin tends to vary inversely with the amount of thyroid per kg. of body weight. Also the colloid tends to vary inversely between the amount of colloid and the amount of thyroid per kg. of body weight.

Marked Glandular Hyperplasias.—In general the amount of thyroid per kg. of body weight tends to vary inversely with the amount of iodin, but to this there are some exceptions. There seems to be no relation between the iodin content and the amount of colloid, though the amount of visible colloid is so small that accurate estimations are impossible. The amount of colloid tends to run parallel with the amount of thyroid per kg. of body weight, but with rather numerous exceptions.

Summary of the Relation of the Iodin Content, Size of Thyroid, and Quantity of Colloid.

In Table 6 the amount of iodin is found to vary inversely with the amount of thyroid per kg. of body weight, and the amount of iodin in the colloid varies inversely in the normal and colloid glands. In the

TABLE 6.—A. Based on the Averages from Table 5.

Character of Glands.	Iodin to Thyroid per kg. of Body Weight.	Iodin to Colloid.	Colloid to Thyroid per kg. of Body Weight.
(1) Normals and colloids	Inverse	Inverse	Direct
(2) From normals through hyperplasias	Inverse	Direct	Inverse

B. Based on the analyses of the individual glands of the separate groups and intermediates, as described in the preceding section.

Character of Glands.	Iodin to Thyroid per kg. of Body Weight.	Iodin to Colloid.	Colloid to Thyroid per kg. of Body Weight.
(1) Normals	Inverse	Inverse	Direct
(2) Colloids	Inverse	Inverse	Direct
(3) Normal X early	Inverse	Direct	Inverse
(4) Early	Inverse	No relation	Inverse
(5) Moderate	Direct (?)	Direct	No relation
(6) Moderate X marked	Inverse	Inverse (?)	No relation
(7) Marked	Inverse	No relation	Direct

hyperplasias the amount of iodin also varies inversely with the amount of thyroid per kg. of body weight, but the amount of iodin in the colloid varies directly with the colloid. In the normal glands and in the colloids the amount of colloid in 1 gm. of fresh thyroid compared with the amount of thyroid per body weight seems to vary directly, while in the hyperplasias it varies inversely.

Comparing these conclusions with those of the analyses of the individual glands of the separate groups, a general agreement is found; that is, these changes are evident not only when whole groups are compared, but when the gradations of the individual members of the groups are compared. The agreement is not, however, absolute in detail. From Table 6-B it will be seen that the results in the separate groups agree with those of the averages in eight instances and are contrary in three. Similarly, within each group, individual exceptions are noted. It appears evident, therefore, that other factors than iodin are concerned which are not taken into account in our observations. In some of the cases at least the factors were plainly accidental, such as hemorrhage, cysts, etc.

However, the very striking fact that the same general laws hold good for the individual cases as well as for the whole group proves that iodin is the predominant objective factor.

(3) *Effects of Weight, Age, Sex, Nutrition and Breed on the Iodin Content.*—(a). The amount of normal thyroid per kg. of body weight is about 0.35 gm., while in our groups it averaged 1.07 for the colloids, 0.30 gm. for the early glandulars, 0.92 gm. for the moderates, and 2.34 for the marked glandular hyperplasias.

(b) Age in relation to iodin content. Thirteen of the sixty-seven glands used in the tables were from dogs under 6 months of age, and show a distinctly low percentage of iodin. In this connection it might be recalled that Baumann found that children at birth rarely had any iodin in the thyroids and that with years the quantity progressively increased, being greatest between the ages of 25 and 45 and diminishing again in old age. Six glands in our series were marked "old," but show no definite change.

(4) Nutrition is probably of more importance than is here indicated, since practically all dogs were in good health. As a rule, the very marked cases of glandular hyperplasia occur in the young and are associated with a greatly reduced iodin content or none at all.

(5) Breed is an indeterminable factor in our cases.

(6) Intercurrent factors. Two pregnant bitches were included in our series; these showed no definite change in iodin content.

EXPERIMENTAL OBSERVATIONS.

(1) *Effect of Feeding Iodin Containing Substances* (Table 7).—In the six cases one lobe was removed as a control, and then different iodin-containing substances were administered in known quantities to ascertain the rapidity of assimilation and the amount stored, as well as to determine what changes occurred in the histologic structure of the gland and the rapidity of these changes. The iodin was administered in the following forms: Saturated alcoholic solution of iodin; syrup of the iodid of iron; desiccated thyroids (commercial); fresh sheep thyroids (all degrees of glandular hyperplasia); full mixed diet (constant factor in all).

As regards the changes in the size of the gland, all the hyperplastic glands show a remarkable reduction in the weight of the remaining lobe, which conforms with the vast clinical observations on man and animals; and, within limits, this occurs without apparent relation to the forms in which the iodin is administered. On the other hand, the normal and colloid glands show no diminution in size.

TABLE 7.—Experimental — Iodin Feeding.

No. of Dog.	Weight of Dog. Kg.	Weight of Fresh Thyroid.	Weight of Dried Thyroid.	Character of Gland.	†Total Iodin.	Iodin per Kg. of Body Weight.	Iodin per Gm. of Fresh Thyroid.	Iodin per Gm. of Dried Thyroid.	Remarks.
26a	2.4	0.21	0.04	Normal . .	0.092	0.038	0.380	2.3	15 gtt. sat. alc. sol. iodin in 13 days; 27 days before death.
26b	4.0	0.305	0.06	Normal . .	0.215	0.053	0.705	3.467	
51a	3.2	22.1	4.47	Colloid. . .	3.16	0.987	0.138	0.707	6 5-gr. thyroid tablets in 3 days; 2 days before death.
51b	3.0	23.1	5.85	Colloid. . .	5.669	1.889	0.245	0.969	
16a	5.0	4.15	0.714	Moderate .	0.061	0.012	0.014	0.086	65 5-gr. thyroid tablets in 13 days; 14 days before death.
16b	3.2	2.7	0.61	Colloid. . .	1.061	0.331	0.393	1.739	
18a	5.4	7.5	1.63	Moderate .	0.425	0.076	0.056	0.261	545 gms. fresh sheep thyroid in 10 days; 8 days before death.
18b	3.18	4.75	1.25	Colloid. . .	6.018	1.889	1.265	4.184	
52a	2.7	3.6	0.52	*Moderate Marked	0.215	0.079	0.057	0.412	15 gtt. sat. alc. sol. iodin in 3 weeks; 2 days before death.
52b	2.8	2.0	0.51	Colloid. .	1.63	0.563	0.815	3.196	
35a	7.27	72.0	13.15	*Moderate Marked.	0.61	0.083	0.008	0.054	7 gtt. sat. alc. sol. iodin in 7 days; 1 day before death; died suddenly; embolus.
35b	6.36	57.2	11.97	Moderate .	16.746	2.633	0.292	1.399	

* Moderate marked glandular hyperplasia.

† Iodin is expressed in milligrams.

The histologic changes in all the hyperplastic glands show a return to the colloid type. In our experience this reversion takes place in about two or three weeks, when there is an excess of iodin present. None of the cases, including the normal glands, show any hyperplasic changes even though the period of forty days, which Halsted advised to allow for the occurrence of hyperplasia, was permitted to elapse.

The total iodin in the control thyroid was invariably much less than the total iodin in the lobe removed after feeding iodin. The amount of iodin assimilated does not seem to be so much dependent on the form in which it is administered as on the amount of glandular tissue present.

It is interesting to note that the iodin content of the colloid of normal glands can be much increased, and also that the colloid from colloid goiters can have its iodin content increased to the same extent. In one dog (A-17), not included in the table, one thyroid lobe was removed during pregnancy. It weighed 0.7 gm. and histologically showed early hyperplasia. The remaining lobe was removed at the end of pregnancy, the dog having received 0.2 gm. of iodin. The lobe weighed 0.65 gm., and histologically was a pure colloid. The iodin in this gland per gm.

TABLE 8.—Experimental—Without Iodin Feeding.

No. of Dog.	Weight of Dog.	Weight of Fresh Thyroid.	Weight of Dried Thyroid.	Character of Gland.	Total mg. Iodin.	Iodin per Kg of Body Weight.	Iodin per Gm. of Fresh Thyroid.	Iodin per Gm. of Dried Thyroid.
27a	1.85	0.25	0.07	Normal.	0.062	0.033	0.248	0.886
27b	1.53	0.15	0.025	Early.	0.038	0.024	0.253	1.520
63a	12.7	14.25	3.41	Colloid.	4.249	0.334	0.298	1.246
63b	12.7	14.0	4.03	Colloid.	1.302	0.102	0.092	0.323
95a	5.9	5.1	1.2	Colloid.	1.284	0.218	0.251	1.076
95b	5.67	3.4	0.77	Colloid.	0.554	0.097	0.163	0.719
64a	2.7	2.25	0.36	Early.	0.108	0.005	0.051	0.300
64b	4.1	2.3	0.41	Colloid.	0.954	0.332	0.415	2.326
94a	2.15	1.5	0.28	Early.	0.184	0.085	0.122	0.657
94b	1.95	1.0	0.21	Early.	0.215	0.110	0.215	1.024
74a	5.44	3.6	0.5	Moderate.	0.261	0.048	0.072	0.521
74b	6.35	2.8	0.55	Early.	0.799	0.125	0.275	1.452

was 1.093 mg., which is above the average for a normal gland. Specimens of liver and muscle showed no trace of iodin.

(2) *Effect of Removing One Lobe Without Administration of Iodin* (Table 8).—In the six dogs one lobe was removed as a control, and the dogs were then kept on the usual laboratory diet (bread, cooked meat, salt and water) without the direct administration of iodin. All show reduction in the size of the remaining lobe, manifested most particularly in the hyperplasic glands, but not as great as is noted in the dogs which had received iodin. The colloids also show some reduction in size, but to a less extent.

Dog 27a was used as the control for 26a. They were sisters and both had normal control lobes. The second lobe of 27a showed the usual compensatory hypertrophy (Halsted), while the second lobe of 26a remained normal in type, though it grew somewhat in size.

The colloid glands showed no histologic evidence of hypertrophy, although chemically they did show evidence (i. e., a reduction in the iodin content). All the hyperplasic glands showed some evidence of reversion, but it was very slight compared with that occurring in the dogs which had been fed iodin. The normal and colloid glands both fell off rapidly in their iodin content, in sharp contrast to those fed iodin. On the other hand, however, the hyperplasic glands showed a slight in-

crease in the iodin content, though much less than in those where iodin had been fed.

This suggests that keeping the dogs on the same diet, the hyperplasic (hyperactive) glands are more capable of taking up iodin than are the more inactive normal or colloid glands.

When we consider dogs 26 and 27 along with dogs 7, 9 and 11, and in connection with the general experimental evidence thus far obtained from various investigators, it further suggests that there is a minimal normal amount of thyroid tissue and a minimal normal amount of secretion necessary for the normal body economy, which is dependent on the available supply of iodin, i. e., the greater the supply of iodin the less the necessary amount of thyroid. This suggestion is further supported by the fact, first pointed out by Halsted, that it is possible to produce goitrous pups by the partial removal of the mother's thyroid, when she is kept on the ordinary diet. We have in addition, experimentally shown[34] that this can not occur in the presence of full amounts of iodin.

OBSERVATIONS ON THE IODIN CONTENT OF THE THYROID GLANDS OF OTHER ANIMALS.

Since it has been shown by many observers that in goitrous districts all mammals are, to a greater or lesser extent, prone to thyroid changes, it is proper that tables be made both of their anatomic changes and their iodin contents in order that the physiologic importance of iodin can be estimated. Though we have merely begun this task, the results may be hinted at and suggestions made.

Human Examinations. — Of two cases anatomically classified as "colloid X early," glandular hyperplasia, one was clinically normal and contained 0.208 mg. of iodin per gm. of fresh thyroid, while the other case was an old colloid goiter on which was engrafted an early hyperplasia. This case was clinically regarded as early exophthalmic goiter engrafted on an old colloid goiter. The gland contained 0.162 mg. iodin per gm. of fresh thyroid. In these two cases the anatomic changes and their iodin contents agree and are similar to the findings in dogs. Of four other cases clinically regarded as exophthalmic goiter (mild cases), who had, however, been treated with iodin, all were anatomically pure colloid goiters and showed iodin contents of 0.304, 0.633, 0.707, 0.883 mg. respectively, thus agreeing with the observations of the others on the rapid storage of iodin, and also agreeing with our anatomic observations indicating that there is a return to the colloid type on the admin-

34. Cleveland Med. Jour., February, 1908, vii, 105.

istration of continued minute doses of iodin even in the exophthalmic hyperplasias.

Sheep.—An hyperplasia which had undergone spontaneous reversion contained 0.455 mg. iodin per gm. of fresh thyroid, while four marked hyperplasias showed in two cases no estimatable amount, and in the other two iodin contents of 0.014 and 0.019 mg. per gm. of fresh thyroid respectively. These observations suggest that here, too, the iodin was proportional to the colloid, and inversely proportional to the degree of glandular hyperplasia.

Horses.—Two thyroids in the anatomic stage of moderate glandular hyperplasia showed 0.054 and 0.091 mg. iodin per gm. of fresh thyroid respectively.

Calves.—A large parenchymatous goiter in the stage of marked glandular hyperplasia contained 0.042 mg. iodin per gm. of fresh thyroid.

Cat and Bear.—On examination a histologically normal cat's thyroid showed 0.154 mg. of iodin per gm. of fresh gland, while the thyroid from a young bear in the stage of early hyperplasia contained 0.081 mg. iodin per mg. of fresh gland.

These observations, though still scanty, suggest that other animals in general obey laws similar to those found for the dog, and also, as pointed out by Baumann, that different animal species have normally different iodin contents—the carnivora having considerably less than the herbivora.

In reviewing the investigations of Baumann, Roos, Oswald and Weiss we find that direct comparisons with our work are impossible, because the methods of iodin determinations differed in some details, but especially because no histologic classification was used, which renders it impossible to estimate what relation iodin bore to the gland structure. However, a summary of their results may be of interest. Baumann and Roos,[35] working with sheep's thyroids, found that their iodin content varied with the regions from which the glands were taken, being least in the goitrous regions, e. g., Frieburg glands contained 1.06 mg. per gm. of dried gland; Elberfelt glands contained 3.40 mg. per gm. of dried gland; Paris glands contained 1.70 mg. per gm. of dried gland.

Baumann,[36] working with human glands, found the same regional differences in the iodin content of normal adult glands as was noted for sheep, e. g., Hamburg glands contained 0.83 mg. iodin per gm. of dried

35. Ztschr. f. physiol. Chem., 1895-6, xxi, 480.
36. Ztschr. f. physiol. Chem., 1896-7, xxii, 1.

gland; Berlin glands contained 0.90 mg. iodin per gm. of dried gland; Freiburg glands contained 0.33 mg. iodin per gm. of dried gland.

He also found that the same differences held for infants and children. In goiters obtained in Freiburg he found 0.09 mg. per gm. of dried gland to be the average iodin content. From these observations he concluded that thyroids from animals in goitrous districts have normally less iodin than glands from non-goitrous regions, and that in uncomplicated goiters it was exceedingly low.

Oswald,[37] working with normal (?) glands from the several provinces of Switzerland, found that the glands contained as much iodin (0.916 mg. per gm. of dried gland) as normal glands from non-goitrous districts, but that goiters (glands weighing 95 gms. or more) contained, on the average, about half as much iodin per gm. of dried thyroid. Weiss[38] found the average iodin content in human glands to be 0.56 mg. per gm. of dried glands for Silesia.

OBSERVATIONS ON THE IODIN CONTENT OF OTHER TISSUES.

From the examination of the livers and muscles in three cases, in two of which iodin had been administered, the thyroids showing a high iodin content, only the slightest possible trace of iodin was present in two pieces of muscle, and none in the livers. We think these findings suggest that the amount of iodin normally present in tissues other than the thyroid is a negligible quantity.

Recently Loeb,[39] from a rather extensive study of the tissues (rabbit) after the administration of known quantities of potassium iodid, arrived at similar conclusions., viz., that after ninety-six hours following the administration of KI to rabbits, mere traces only could be detected in the lungs, kidneys, skin and blood.

If Justus'[40] contention that iodin is present in all cell nuclei be true, it must be so small in amount that it is not determinable by the methods adopted by us. In one case in which two accessory thyroids were examined, an animal to which small amounts of iodin had been administered, a rather high iodin content (0.1 mg.) was found. This is to be expected, since the accessory thyroids (examined histologically in a large number of cases) show similar anatomic changes to those occurring in the main lobes.

The thymus from the same case also showed a relatively large amount

37. Ztschr. f. physiol. Chem., 1897, xxiii, 265.
38. Münch. med. Wchnschr., 1897, xliv, 6.
39. Arch. f. exp. Path. u. Pharmakol., lvi, 320.
40. Virchow's Archiv., Bd. clxx, S. 501.

(0.046 mg.) of iodin. Gross inspection of the gland as well as study of the portions taken for microscopic examination, failed to reveal accessory thyroids. This is at variance with Cunningham and Mendel,[41] who claim that when iodin is present in the thymus it is probably due to the presence of accessory thyroids. In fairness, however, it may be stated here that there is another possible explanation of the presence of iodin in the dog's thymus, viz., that over 20 per cent. of the dogs show persistent cystic dilatation of the embryonal thymic ducts (first described by Remak), and that the iodin present may be the result of excretion into these spaces rather than evidence of its existence in the true functional thymic tissue. Baumann[42] was the first to point out that the thymus contained iodin. He also showed that by feeding dogs with fresh thymus, as compared with feeding with fresh muscle,[43] the iodin content could be raised; this could also be done in the case of thyroid glands by feeding with dog biscuit or sea fish. That the thymus is in many ways related to the thyroid in function has been pointed out by many observers from several points of view. For example, Mikulicz[44] and others have noted the mildly beneficial effects of feeding thymus in goiter; it has also been pointed out that in parenchymatous goiter and in cretins the thymus is generally persistent or even enlarged.[45]

Whether iodin is in any way related to the therapeutic value of thymus or its associated persistence in cretinoid states is a subject on which one of us (Marine) is now collecting data.

OBSERVATIONS ON COMMERCIAL DESICCATED THYROID.

As pointed out in a previous paper by one of us, a large proportion of the sheep in certain districts have enlarged (hyperplastic) thyroids, and it occurred to the writer to visit one of the larger commercial laboratories where desiccated thyroid is prepared to see what kind of glands were being used. It was found that they were using hyperplastic as well as normal glands in preparing their medicinal products. In the light of the findings of Baumann, Oswald, Roos and the authors, viz.: (1) that the iodin content, in general, varies with the amount of colloid; (2) that in general the colloid varies inversely with the degree of glandular hyperplasia; (3) that the iodin content varies inversely with the degree of glandular hyperplasia, and (4) that the physiologic activity

41. Am. Jour. Physiol., 1900, iii, 285.
42. München. med. Wchnschr., 1896, liii, 311.
43. Ztschr. f. physiol. Chem., 1896-7, xxii, 14.
44. Berl. klin. Wchnschr., 1895, xxxii, S. 342.
45. Marie, Gaz. d. hôp., 1893, p. 202; also Hektoen, Internat. Med. Mag., 1896, iv, 584.

of thyreoglobulin varies directly with the amount of iodin in organic combination, it becomes necessary to determine the iodin content of the various thyroid preparations. Accordingly, one of the firms prepared for us samples made from what they considered (1) normal glands (gross appearance), and (2) hyperplastic glands (gross appearance). We add the iodin contents of these specimens, and for comparison the iodin contents of a sample obtained in the market, together with a determination made from histologically normal glands.

Specimen "C" from hyperplastic glands,, 0.292 mg. iodin per gm. of dried gland; specimen "D" from normal glands, 1.092 mg. iodin per gm. of dried gland; specimen "E" obtained in the market, 1.538 mg. iodin per gm. of dried gland; specimen "F" histologically normal glands, 1.769 mg. iodin per gm. of dried gland.

These four analyses indicate that the preparation made from the hyperplasias contains only one-sixth the amount of iodin present in the histologically normal glands, while a sample obtained in the market contained a third more iodin than the sample made from supposedly normal glands. There being no reason to suppose that iodin was added, no attempt was made to determine whether there was any free iodin. Since the manufacturing firms use both the hyperplastic and the normal glands in the preparation of their therapeutic products, it follows that different samples must contain varying amounts of iodin. Aufrecht examined thyroid tablets made from hog's glands obtained from different localities and found great variations in the iodin content.

Experiments with feeding specimens "C" and "D" desiccated thyroid were undertaken and, although accidentally incomplete, are suggestive enough to be mentioned here. Two dogs (A-107 and A-108) of the same age, breed and weight were fed on equal amounts (11 gms.) of specimens "C" and "D" respectively in eighteen days. The dog fed with specimen "C" (hyperplasia) did not lose weight, and the amount of iodin per gm. of fresh thyroid was 0.173 mg. (gland taken twenty-one days after last dose of substance); while the other dog (A-108) fed on specimen "D" (normal glands) lost 454 gms. in weight in eighteen days of feeding; the amount of iodin per gm. of fresh thyroid was 0.439 mg. (gland taken twenty-one days after last dose). This suggests, as Oswald and Roos have pointed out, that the activity of the thyroid substance varies with the amount of iodin in organic combination; but it is not in contradiction with the possibility and, indeed, the probability,

as mentioned by Hunt[46] and one of us,[1] that the substance, in the absence of iodin, may have other activities.

GENERAL DISCUSSION.

The importance of a histologic basis of classification in goiter can not be overestimated. Virchow, as early as 1863, pointed out the great confusion which then existed in the classification of thyroid diseases and also the dangers to which it was leading, viz., the interference with the advance in our knowledge of goiter both anatomically and clinically. In the first place, the classification must be rigid, and second, it must be dependent on the three natural anatomic divisions., viz., (1) normal glands; (2) colloid glands; (3) hyperplasia. In an organ whose structure is so manifestly affected by a variety of systemic conditions it is clearly impossible to make use of any other factor than anatomy as a point of departure. Little need be added relative to the anatomic descriptions of the groupings already given. It is to be regretted that more normal glands were not found, though it seems unlikely that iodin determinations in a larger number of normal glands would have materially changed the relative importance, and it is this feature, rather than the actual figures, that we consider important.

Comparison of the iodin determinations with the corresponding histologic groupings, as shown in Tables 2, 3, 4 and 5, permit the deduction of several important general conclusions which bring the relationship of iodin to the structure of the thyroid closer than has heretofore been suspected. Some of these relationships may be again referred to, for the sake of emphasis: the percentage of iodin in general varies with the amount of stainable colloid, as was first pointed out by Oswald. To this rule there is an apparent contradiction in the normal and colloid gland, but this can be explained by the fact that there are quite wide limits in the percentage of iodin above the amount necessary for the maintenance of normal structure, and this reserve iodin, so to speak, produces no detectable microscopical changes. It also appears to be a general law that the colloid material in general varies inversely with the degree of glandular hyperplasia, and third, it is shown that the iodin content varies inversely with the degree of glandular hyperplasia.

In the analyses of the individual members of the separate groups there are many apparent exceptions also to the last two general laws mentioned, and these exceptions rather suggest that while iodin is the main object and factor governing thyroid activity, there are other con-

46. The Journal A. M. A., 1907, p. 1323.

ditions as well which influence the gland structure. This, indeed, would be probable if goiter is considered as a manifestation of a nutritional disturbance.

As pointed out above, there are wide variations between the amount of iodin necessary to maintain normal structure and the largest amount which can be held in organic combination by the colloid (thyreoglobulin), and within these limits the microscopic changes in the structure are too slight to be estimated accurately, though there must be wide differences in structure that are not to be detected by present microscopic methods. In view of this factor of error in normal and colloid glands, more importance should be attached to the early hyperplasias and to the minimal amount of iodin necessary to start hyperplastic changes. This minimal amount is found to be quite constant, as shown in Table 5, being 0.173 mg. iodin per gm. of fresh thyroid for the "normal X early" glands, 0.217 mg. for the "colloid X early," and 0.139 mg. for the pure early glands.

Passing to the hyperplasias, here, too, we find a difficult factor to determine by histologic examination for the reason that microscopically it is often difficult to decide whether a gland is reverting from a more marked hyperplasia or is undergoing secondary hyperplasia; in the former case the iodin content would be higher than in the latter. So that, in view of these known difficulties, it is probable that future workers, while laying most stress on the anatomic structure, will have to take cognizance of the iodin content as well, in order to group the glands accurately and to estimate their functional activity. Nevertheless, it is clear that these apparent exceptions do not materially affect the importance established for iodin in its relation to thyroid structure and gland activity, and, besides, it is probable that all these exceptions could be rationally explained if the complicating factors acquired during the life of the animal were known.

A point worthy of special notice is that the iodin contents of the glands included under double references, as shown in Table 5, fall between the iodin contents of the groups to which they were anatomically referred, though in making up the original tables they were not considered at all, and the results could not in any way be influenced by ideas gained from the original (pure) groups. This additional grouping amounts, in effect, to doubling the evidence in proof of the three laws above mentioned, and also indicates that the hyperplasias, both histologically and chemically, resist arbitrary grouping, but represent a continuous gradation from the normal glands to the marked hyperplasias.

In a previous paper[1] it has been pointed out that the thyroid is not the only tissue affected in the production of glandular hyperplasia (parenchymatous goiter). As has been pointed out by many observers, the lymphoid tissues (spleen, thymus and lymph glands), together with the bone marrow, show quite constant lesions that must be considered integral parts of the general disturbance, and when one recalls the experimental biologic data already mentioned in the introduction it appears highly probable that in the natural occurrence of goiter, as in its artificial production, the underlying process is essentially a "compensatory reaction to some deficiency" rather than that it is a spontaneous thyroid affection. This is a view quite opposite to that held by many students of exophthalmic goiter. That iodin is the most important single factor in this disturbance is further suggested by the fact that the ability of the thyroid to store iodin depends on the degree of glandular hyperplasia rather than on the form or mode of its administration, as shown in Table 9, and also that there is an economy and storage of iodin (somewhat comparable to that of iron), as shown by the fact that there are wide limits in the iodin content between the amount necessary to maintain normal structure and the highest amount of iodin which can be stored in the gland.

In view of the evidence thus far deduced, we believe that goiter must be classed with the nutritional disturbances (diseases) and that as such it will take its place in nosology along with chlorosis, rachitis, status lymphatics, osteomalacia, (?) etc. That there are other factors than iodin influencing the thyroid changes seems to be proved, but there is no experimental evidence that a specific infecting agent as such is one of these factors.

The mode of action of iodin is probably similar to that of iron, calcium and other normal metallic constituents of the body in their relations to normal and disturbed metabolism, viz., that as in the case of iron, calcium, etc., so with iodin, (1) the body practices an economy in its use; (2) there is a normal minimal amount necessary for the body needs, and a variable reserve quantity, and (3) that a deficiency of either element induces anatomical changes in the tissues directly concerned with their storage and elaboration.

Finally, the treatment of simple hyperplasias has close analogies with the treatment of chlorosis, particularly in that the form of iron or iodin administered is not all important, since the ability to take up these metals depends rather on the degree of tissue reaction. And this fact suggests a point in the treatment of symptomatic thyroid hyperplasias

that may have considerable practical importance, viz., that the physiologic dose of iodin should be inverse to the degree of glandular hyperplasia.

The reversion to a colloid type, which occurs coincidently with the administration of iodin in a hyperplasia, is the histologic evidence of a cure and not of a degenerative process in the usual interpretation of that term. Colloid glands (goiters) are the nearest normal condition to which the hyperplasias can return, and not only is this true of their gross and histologic appearance, but also of their chemical (iodin) and clinical bearing as well.

The problem of commercial desiccated thyroid is an important one for the pharmacologist and clinician alike, as has already been shown both on the bases of anatomic structure of the thyroids used and on its physiologic activity. Some standard, either chemical or physiologic, is needed, even if in the absence of organically combined iodin the substance is inert. This, however, can not be granted at present, as there is some clinical evidence that these hyperplastic glands during life have a greatly altered secretion which exerts a toxic action on the organism. Whether this activity may be destroyed in the preparation of desiccated thyroid is a very important problem for clinical experiment, particularly when desiccated thyroid is so extensively used in the treatment of thyroid changes histologically similar to those existing in the glands from which the preparations are made.

PROBLEMS OF HUMAN GOITER.

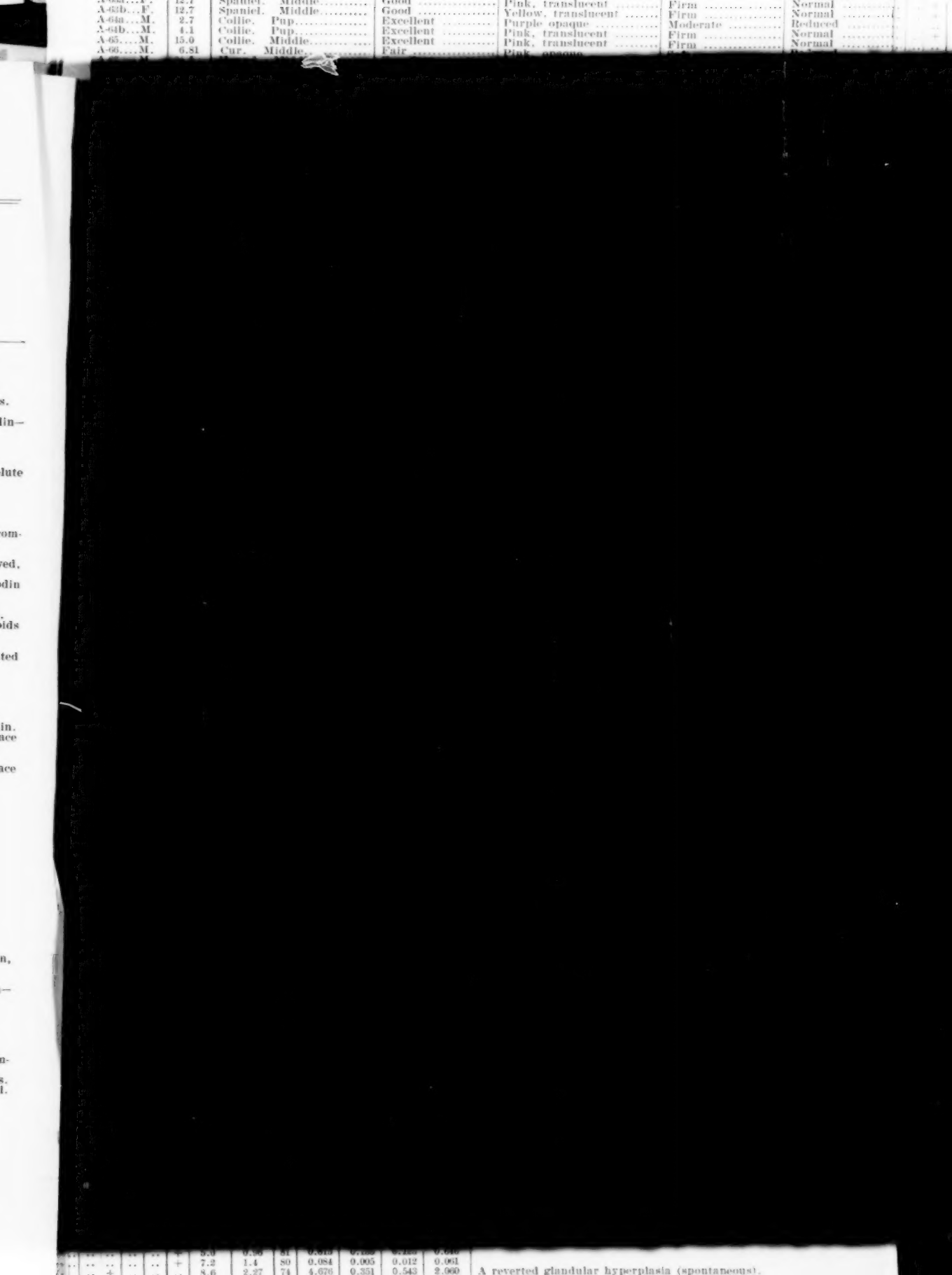
In view of the relations that have been shown to exist between the amount of iodin and the histologic structure of the thyroid in the dog, and in view of the facts thus far collected as to the incidence, distribution, nature and treatment of goitrous conditions in all animals, it seems necessary that similar work be carried out in man, both in goitrous and non-goitrous districts. The essential problems for solution must be the same in man as in animals, and are modified only by man's position in the biologic scale and by the vast complex of acquired conditions—accidental or intentional (social complex, food, migration, locality, medication, etc.).

With fairly definite anatomic criteria established in animals, it seems possible to group and study the human forms. This work is now in progress. As is to be expected, great irregularities are met with on account of complicating factors which are almost always present and make interpretation of the observations difficult. However, the general conditions so far are found to obey the same general laws that were

TABLE 9.—TO ACCOMPANY ARTICLE BY DAVID MARINE, M.D., AND W. W. WILLIAMS, M.D., ON RELATION OF IODIN TO THE STRUCTURE

No. of Dog and Sex.	Weight	Breed and Age.	Macroscopic.				Microscopic.					Chemic					
			Nutrition.	Color.	Consistency.	Colloid.	Normal.	Colloid.	Glandular Hyperplasia. Early.	Moderate.	Marked.	Weight fresh thyroid.	Weight dried thyroid.	Percent. water.	Total iodin.	Iodin per kg body weight.	Iodin per gm. fresh thyroid.
A-1....M.	3.63	Collie. Young.....	Good	Yellow-pink, translucent..	Firm	Normal	+?	..	+	..	..	1.0	0.2	80	0.181	0.051	0.018
A-2....M.	9.09	Spaniel. Middle.....	Fair	Gray, fleshy	Soft	None	..	..	..	..	..	59.0	18.7	68	0.837	0.091	0.014
A-3....M.	6.36	Collie. Middle.	Fair	Pink, opaque	Moderate	Reduced	..	..	..	..	+	7.0	1.46	79	0.292	0.062	0.042
A-4....M.	8.2	Terrier. Middle.....	Fair	Gray-pink, fleshy	Soft	None	..	..	..	..	..	1.3	0.31	76	0.039	0.011	0.017
A-5....M.	11.81	Fox terrier. Middle.....	Excellent.....	Pink	Moderate	Reduced	..	..	..	..	+	7.0	1.46	79	0.292	0.062	0.042
A-6....M.	8.2	Terrier. Middle.....	Moderate	Yellow-pink	Firm	Reduced	..	..	..	..	..	*1.0	0.46	84	0.123	0.018	0.045
A-7....M.	15.9	Scotch terrier. Middle...	Excellent	Yellow, translucent	Firm	Normal	..	..	+	..	..	1.7	0.36	79	0.153	0.015	0.073
							..	..	+	..	..	*2.85	1.15	70	0.140	0.198	0.412
A-8*...F.	10.0	Bull terrier. Middle.....	Excellent	Yellow, translucent	Firm	Abundant	..	+	..	..	..	51.9	16.9	69	26.769	2.676	0.487
A-9....M.	9.98	Scotch terrier. One year.	Excellent	Pink, fleshy.....	Moderate	None	..	..	..	..	+	*1.05	0.23	78	0.031	0.003	0.029
A-10....M.	5.9	Terrier. Young.....	Fair	Pink, fleshy	Soft	None	..	..	..	..	+	77.9	15.1	80	1.430	0.242	0.018
A-11....M.	8.4	Fox terrier. Middle.....	Excellent	Yellow, translucent	Firm	Abundant	..	+	..	..	..	*4.55	1.35	70	2.087	0.248	0.458
A-12....M.	20.86	Bulldog. Young adult...	Good	Fleshy red	Soft	None	..	..	..	..	+	39.35	7.32	81	2.701	0.128	0.068
A-13....M.	9.10	Terrier. Middle.....	Fair	Brown-red, translucent ...	Moderate	Normal	..	+	..	..	..	20.45	5.57	73	5.224	0.574	0.255
A-14....F.	9.5	Cur. Middle.....	Fair	Gray-pink, vascular	Soft	None	..	..	..	..	+	4.75	0.70	85	0.332	0.034	0.070
A-15....M.	15.60	Collie. Middle.....	Good	Gray-pink, fleshy.....	Soft	None	..	..	..	..	+	3.20	0.54	83	0.092	0.005	0.019
A-16a...M.	5.0	Terrier. Old.....	Fair	Gray-pink, fleshy.....	Soft	None	..	..	..	..	+?	*4.15	0.714	82	0.061	0.012	0.014
A-16b...M.	3.2	Terrier. Old.....	Emaciated	Yellow, translucent.....	Firm	Normal	..	+	+?	..	..	*2.70	0.61	77	1.061	0.331	0.393
A-17a...F.	5.4	Dachshund. Middle.....	Good	Gray-yellow, translucent.	Firm	Normal	+	..	+	..	..	0.70	0.162	72			
A-17b...F.	5.0	Dachshund. Middle.....	Good	Clear yellow	Firm	Normal	..	+	..	..	..	0.65	0.135	79	0.027	0.121	1.031
A-17c...F.	0.210	Daughter of A-17b; 3 days.	Good	.....	.....	Normal	+	..	..	..	..	0.01	0.002	80			
A-18a...F.	*5.4	Terrier. Middle.....	Fair	Gray-pink, fleshy	Soft	None	..	..	+	..	..	*7.5	1.65	78	0.495	0.076	0.066
A-18b...F.	3.18	Terrier. Middle.....	Emaciated	Clear-yellow, translucent.	Firm	Abundant	..	+	..	..	..	*4.75	1.25	83	0.918	1.869	1.205
A-19....F.	2.5	Terrier. Middle.....	Poor	Pink, fleshy	Soft	None	..	..	..	..	+	12.29	2.25	81	0.023	0.009	0.001
A-20....M.	5.6	Bull terrier. Pup.....	Excellent	Yellow, translucent.....	Firm	Abundant	..	+	..	..	..	*27.9	6.95	75	15.420	2.751	0.985
A-21....M.	9.0	Hound. Middle.....	Fair	Pink, fleshy.....	Moderate	Reduced	..	..	..	+	..	2.3	0.6	74	0.061	0.006	0.026
A-22....F.	?	?	?	Yellow-pink	Firm	Reduced	..	..	..	+	..	5.1	1.65	68	0.425	?	0.082
A-23....F.	4.5	Terrier. Old.....	Fair	Pink	Moderate	None	..	..	..	+	..	5.0	0.96	81	0.615	0.123	0.123
A-24....M.	15.9	Spaniel. Middle.....	Fair	Pink, fleshy.....	Soft	None	..	..	..	+	..	7.2	1.4	80	0.084	0.005	0.012
A-25....M.	11.3	Hound. Middle.....	Fair	Yellow, pink.....	Firm	Normal	..	+	..	..	..	8.6	2.27	74	4.626	0.551	0.543
A-26a...F.	2.4	Terrier. Pup.....	Fair	Yellow, pink.....	Firm	Reduced	+	..	..	..	..	*0.24	0.04	83	0.092	0.038	0.380
A-26b...F.	4.0	Terrier. Pup.....	Excellent	Clear, yellow, translucent.	Firm	Normal	+	..	..	..	..	*0.205	0.06	80	0.215	0.054	0.705
A-27a...F.	1.85	Terrier. Pup.....	Fair	Yellow-pink	Firm	Reduced	+	..	..	..	..	*0.25	0.07	72	0.062	0.045	0.248
A-27b...F.	1.53	Terrier. Pup.....	Emaciated	Yellow-pink	Firm	Reduced	+	..	+	..	..	*0.15	0.025	83	0.058	0.024	0.253
A-28....M.	11.3	Terrier. Middle.....	Good	Pink, fleshy	Soft	None	..	..	..	..	+	8.1	1.54	82	0.055	0.005	0.004
A-29....M.	5.4	Collie. Pup.....	Good	Red, fleshy	Soft	None	..	..	..	..	+	4.8	0.44	88	0.053	0.009	0.001
A-30....F.	14.5	Bull. Middle.....	Fair	Yellow-pink	Moderate	Reduced	..	..	..	+	..	8.25	1.98	76	2.424	0.167	0.293
A-31....F.	9.07	Collie. Pup.....	Good	Yellow, translucent	Firm	Normal	+	..	+	..	..	2.2	0.487	77	0.453	0.069	0.206
A-32....M.	5.9	Beagle. Young.....	Poor	Gray-pink	Moderate	Reduced	..	+	..	+	..	29.8	7.24	75	0.443	0.026	0.015
A-33....M.	8.16	Terrier. Young.....	Good	Pink, fleshy.....	Moderate	Reduced	..	..	..	+	..	25.9	5.75	77	1.324	0.236	0.051
A-34....M.	5.6	Terrier. Middle.....	Fair	Red-yellow	Moderate	Reduced	..	..	..	+	..	4.9	0.72	85	0.043	0.153	0.125
A-35....M.	11.8	Spaniel. Middle.....	Good	Red-opaque	Soft	Reduced	..	..	..	+	..	22.9	5.75	74	1.679	0.143	0.074
A-36....M.	10.0	Terrier. Middle.....	Good	Yellow-pink	Moderate	Reduced	..	..	..	+	..	7.0	2.08	70	1.823	0.182	0.262
A-37....M.	11.0	Hound. Middle.....	Poor	Pink-opaque	Moderate	Reduced	..	..	..	+	..	40.0	11.06	72	4.015	0.365	0.100
A-38....M.	6.3	Bull terrier. Pup.....	Excellent	Clear, yellow, translucent	Firm	Normal	+	..	..	..	..	1.3	0.33	77	0.084	0.065	0.757
A-39....F.	6.3	Terrier. Middle.....	Fair	Gray, translucent	Firm	Normal	+	..	..	..	..	1.7	0.44	74	0.108	0.017	0.063
A-40....M.	14.0	Setter. Middle.....	Good	Yellow-pink	Firm	Reduced	..	..	+	..	..	4.5	1.184	74	0.780	0.097	0.197
A-41....F.	5.0	Terrier. Pup.....	Poor	Fleshy-pink	Soft	None	..	..	..	..	+	5.8	0.87	85	0.040	0.008	0.008
A-42....M.	12.7	Pointer. Middle.....	Good	Yellow-pink	Firm	Normal	+	..	..	..	..	6.5	1.56	76	1.271	0.100	0.195
A-43....F.	6.0	Terrier. Middle.....	Good	Clear, yellow, translucent	Firm	Normal	+	..	..	..	..	1.25	0.125	90	0.125	0.020	0.100
A-44a...F.	7.7	Hound. Six months....	Poor	Red, gray.....	Moderate	Reduced	..	..	..	..	+	10.0	8.2	78	1.001	0.127	0.025
A-44b...F.	7.7	Hound. Six months....	Poor	Red, gray.....	Moderate	Reduced	..	..	..	..	+	*25.9	5.74	85	0.288	0.027	0.011
A-45a...M.	6.3	Terrier. Middle.....	Good	Pink, opaque.....	Soft	None	..	..	..	..	..	*4.9	0.75	81	0.015	0.002	0.004
A-45b...M.	6.3	Terrier. Middle.....	Good	Pink, opaque.....	Soft	None	..	..	..	..	..	*4.1	0.24	78	0.015	0.002	0.004
A-46....M.	10.4	Bull. Middle.....	Good	Gray, translucent	Firm	None	..	..	..	..	+	3.35	0.685	80	0.007	0.001	0.027
A-47....F.	6.3	Spaniel. Young.....	Good	Pink, opaque.....	Moderate	None	..	..	..	..	..	8.0	1.56	80	0.007	0.007	0.008
A-48....M.	13.6	Terrier. Middle.....	Good	Clear, yellow, translucent	Firm	Normal	..	..	..	..	..	3.1	0.86	72	1.754	0.129	0.566
A-49....F.	5.4	Cur. Middle.....	Fair	Pink, translucent.....	Firm	Normal	+	..	..	..	..	1.7	0.51	70	0.051	0.010	0.153
A-50....F.	17.0	Bull. Middle.....	Good	Pink, translucent.....	Firm	Reduced	..	..	..	..	..	16.1	4.69	70	2.961	0.133	0.185
A-51a...M.	3.2	Terrier. Middle.....	Fair	Pink, translucent.....	Moderate	Reduced	..	..	..	..	..	*22.1	4.42	80	0.885	0.138	0.107
A-51b...M.	3.0	Terrier. Middle.....	Emaciated	Pink, translucent.....	Moderate	Normal	..	..	..	..	..	*24.1	5.83	76	2.859	1.906	0.143
A-52a...F.	2.7	Terrier. Pup	Fair	Pink, opaque.....	Soft	None	..	..	..	..	..	5.0	0.52	85	0.215	0.080	0.097
A-52b...F.	2.8	Terrier. Pup	Good	Clear, yellow	Firm	Normal	..	..	..	..	..	2.0	0.51	75	1.021	0.365	0.510
A-53....F.	9.0	Spaniel. Middle.....	Good	Gray-pink	Moderate	Reduced	..	..	..	..	..	8.1	1.55	81	0.194	0.022	0.024
A-54....M.	5.4	Terrier. Middle.....	Good	Red, opaque	Soft	None	..	..	..	..	..	20.1	3.38	83	0.101	0.019	0.005
A-55a...M.	7.27	Bull. Pup.....	Poor	Purple, opaque	Soft	None	..	..	..	..	..	*22.0	15.13	31	0.330	0.045	0.015
A-55b...M.	6.36	Bull. Pup.....	Poor	Pink, opaque	Soft	None	..	..	..	..	..	*25.2	11.30	55	0.790	0.124	0.031
A-56....F.	7.3	Spaniel. Middle.....	Good	Clear, yellow	Firm	Normal	..	..	..	..	..	1.5	0.28	81	0.112	0.015	0.074
A-57....F.	6.8	Collie. Middle.....	Fair	Pink-yellow	Firm	Normal	..	..	..	..	..	2.1	0.42	80	0.369	0.054	0.175
A-58....F.	5.0	Terrier. Young.....	Poor	Pink, opaque	Moderate	Reduced	..	..	..	..	..	5.82	1.34	77	0.536	0.107	0.092
A-59....F.	11.0	Collie. Old.....	Good	Pink translucent	Moderate	Reduced	..	..	..	..	..	4.29	1.002	76	0.601	0.055	0.140
A-60....F.	5.3	Terrier. Young.....	Good	Pink, opaque.....	Soft	Reduced	..	..	..	..	..	16.97	3.8	78	0.608	0.115	0.036
A-61....F.	4.9	Terrier. Young.....	Good	Pink, opaque.....	Soft	Reduced	..	..	..	..	..	2.0	0.4	80	0.080	0.016	0.040
A-62....M.	7.3	Terrier. Middle.....	Good	Pink, translucent	Firm	Normal	..	..	..	..	..	2.0	0.33	84	0.198	0.027	0.099
A-63a...F.	12.7	Spaniel. Middle.....	Good	Pink, translucent	Firm	Normal	..	..	..	..	..	11.25	2.41	79	0.844	0.066	0.075
A-63b...F.	12.7	Spaniel. Middle.....	Good	Yellow, translucent	Firm	Normal	..	..	..	..	..	*14.0	1.91	87	0.401	0.031	0.029
A-64a...M.	2.7	Collie. Pup.....	Excellent	Purple opaque	Moderate	Reduced	..	..	..	..	..	*2.25	0.56	75	0.056	0.021	0.025
A-64b...M.	4.1	Collie. Pup.....	Excellent	Pink, translucent	Firm	Normal	..	..	..	..	..	*2.5	0.41	84	0.041	0.010	0.016
A-65....M.	15.0	Collie. Middle.....	Excellent	Pink, translucent	Firm	Normal	..	..	..	..	..	4.48	0.89	80	0.534	0.036	0.119
A-66....M.	6.81	Cur. Middle.....	Fair	Pink, opaque.....	.....	.....	..	..	..	..	..	.....	.....	.....	.....	.....	.....

Microscopic.					Chemic.							Remarks.
Normal.	Colloid.	Glandular Hyperplasia. Early.	Moderate.	Marked.	Weight fresh thyroid.	Weight dried thyroid.	Percent. water.	Total iodin.	Iodin per kg. body weight.	Iodin per gm. fresh thyroid.	Iodin per gm. dried thyroid.	
+?	..	+	..	..	1.0	0.2	80	0.185	0.051	0.018	0.927	
..	..	..	..	+	50.0	18.3	69	0.837	0.091	0.014	0.046	Moderate hemorrhagic-cystic change.
..	..	..	..	..	1.5	0.31	79	0.070	0.011	0.047	0.227	
..	..	..	..	+	7.9	1.46	79	0.269	0.032	0.038	0.184	
..	..	..	..	..	*1.9	0.36	81	0.123	0.104	0.045	0.171	*Right lobe removed 1 year ago. Iodin calculated as for 2 lobes.
..	..	..	..	+	1.7	0.36	79	0.123	0.015	0.072	0.345	
..	..	+	..	..	*3.85	1.13	70	3.146	0.198	0.812	2.784	*Right lobe removed 1 year ago. Weight equals 3.85 gm. Iodin—absolute amount.
..	+	..	..	..	54.9	16.9	69	26.760	2.679	0.487	1.584	Uterus and ovaries removed 6 months ago.
..	..	..	..	+	*1.05	0.23	78	0.031	0.003	0.029	0.135	* Right lobe removed 7 months ago. Iodin—absolute amount.
..	..	..	..	+	77.9	15.1	80	1.430	0.242	0.018	0.090	
..	+	..	..	..	*4.55	1.35	70	2.087	0.248	0.458	1.538	*Right lobe removed 1 year ago. Weight 7.2 gms. Iodin—absolute amount.
..	..	..	..	+	39.35	7.32	81	2.701	0.129	0.068	0.369	Desquamation—not included in tables.
..	+	..	..	..	20.45	5.57	73	5.224	0.574	0.255	0.938	
..	..	..	..	+	4.75	0.70	85	0.092	0.014	0.019	0.132	
..	..	..	..	+	3.80	0.54	83	0.062	0.005	0.019	0.114	
..	..	..	+	+?	*4.15	0.714	82	0.061	0.012	0.014	0.086	*Left lobe removed, Jan. 22, 1907. Fed desiccated thyroid (commercial).
..	+	+?	..	..	*2.70	0.61	77	1.061	0.331	0.393	1.739	*Died Feb. 20, 1907. Sixty-five 5-gr. tablets given in 28 days.
..	+	..	..	..	0.70	0.192	72	.....	.....	.....	.....	Iodin not determined—accident. Pregnant right lobe removed, Feb. 20, 1907.
..	+	..	..	..	0.65	0.135	79	0.623	0.124	1.093	4.615	Killed March 15, 1907, 33 days after birth of puppies; 200 mg. iodin given. Bits of liver and muscle showed no trace of iodin.
+	..	..	..	..	0.01	0.002	80	.....	.....	.....	.....	Slightest possible trace of iodin.
..	..	..	+	..	*7.5	1.63	78	0.425	0.076	0.056	0.261	* Left lobe removed Jan. 22, 1907. Dog fed fresh sheep thyroids.
..	+	..	..	..	*4.75	1.25	83	6.018	1.389	1.265	4.184	*Died Feb. 11, 1907. Had taken 545 gms. fresh sheep thyroids (hyperplasias).
..	..	..	..	+	12.22	2.35	81	0.073	0.029	0.006	0.031	
..	+	..	..	..	*27.0	6.95	73	15.429	2.721	0.285	1.110	*Right lobe removed. Fed iodin. Cretinoid dog. Iodin calculated as for 2 lobes.
..	..	..	+	..	2.3	0.6	74	0.061	0.006	0.026	0.101	
..	..	+	+	..	5.1	1.63	68	0.425	?	0.082	0.261	
..	..	..	..	+	5.0	0.96	81	0.615	0.135	0.123	0.640	
..	..	..	..	+	7.2	1.4	80	0.084	0.005	0.012	0.061	
..	+	..	..	..	8.6	2.27	74	4.676	0.351	0.543	2.060	A reverted glandular hyperplasia (spontaneous).
+	..	..	..	..	*0.24	0.04	83	0.092	0.038	0.380	2.30	*Right lobe removed Feb. 15, 1907. Fed 15 gtt. sat. als. sol. iodin.
+	..	..	..	..	*0.305	0.06	80	0.215	0.053	0.705	3.467	*Killed April 2, 1907. Had grown rapidly. Muscle—slightest trace iodin.
+	..	..	..	..	*0.25	0.07	72	0.062	0.033	0.248	0.886	*Right lobe removed Feb. 15, 1907. No iodin administered.
..	..	+	..	..	*0.15	0.025	83	0.038	0.024	0.253	1.52	*Died April 2, 1907. Pneumonia. Iodin—slightest possible trace in muscle.
..	..	..	..	+	8.4	1.54	82	0.035	0.003	0.004	0.023	
..	..	..	..	+	4.8	0.44	88	0.031	0.006	0.006	0.069	
..	+	..	+	..	8.25	1.98	76	2.423	0.167	0.293	1.224	Beginning reversion.
+	..	+	..	..	2.2	0.487	77	0.631	0.069	0.286	1.296	
..	+	..	+	+	29.8	7.24	75	0.449	0.076	0.015	0.062	Probably marked glandular.
..	+	..	+	..	25.0	5.75	77	1.771	0.216	0.071	0.308	Reverting, spontaneously.
..	..	..	+	..	4.9	0.72	85	0.615	0.173	0.125	0.854	
..	..	..	+	..	22.0	5.75	74	1.679	0.142	0.076	0.292	
..	+	..	+	..	7.0	2.08	70	1.823	0.183	0.262	0.784	Reverting, spontaneously.
..	..	..	+	+	40.0	11.06	72	4.015	0.365	0.100	0.363	
+	..	..	..	..	1.3	0.31	77	0.984	0.156	0.757	3.205	
..	..	+	..	..	1.7	0.44	74	0.108	0.017	0.063	0.243	
..	..	+	..	..	4.5	1.184	74	0.890	0.062	0.197	0.752	
..	..	..	..	+	5.8	0.87	85	0.046	0.009	0.008	0.053	
+	..	+	..	..	6.5	1.56	76	1.271	0.109	0.195	0.815	
..	+	..	..	..	1.25	0.115	91	0.415	0.049	0.332	3.608	
..	..	..	+	+	*40.0	8.3	79	1.021	0.132	0.025	0.123	*Right lobe removed March 14, 1907. Gland hemorrhagic.
..	..	..	+	+	*25.0	3.74	85	0.288	0.037	0.011	0.077	*Died, wound infection after 2 days. Half left lobe used for iodin, absolute amount.
..	..	..	..	+	*4.0	0.75	81	0.015	0.002	0.004	0.020	*Right lobe removed, March 14, 1907.
..	..	..	..	+	*1.1	0.24	78	0.015	0.002	0.013	0.062	*Killed, infected, March 16, 1907. Half + l. lobe used for iodin—absolute amount.
..	..	..	..	+	3.35	0.685	80	0.002	0.006	0.027	0.184	
..	..	..	..	+	8.0	1.58	80	0.013	0.002	0.002	0.008	
..	+	..	..	..	3.1	0.86	72	1.753	0.128	0.565	2.033	Considered colloid, using strict classification.
+	..	+	..	..	1.7	0.54	68	0.261	0.048	0.153	0.483	
..	+	+	..	..	16.1	4.69	70	2.021	0.119	0.125	0.431	Spontaneous reversion.
..	+	..	..	..	*22.1	4.47	79	3.160	0.987	0.138	0.707	*Left lobe removed March 29, 1907. Fed desiccated thyroids (commercial).
..	+	..	..	..	*23.1	5.85	74	5.669	1.889	0.245	0.969	*Died April 4, 1907. Pneumonia. Received 6 tablets, each 5 grains.
..	..	..	+	+	*3.6	0.52	85	0.215	0.079	0.057	0.413	*Right lobe removed March 29, 1907. Fed iodin, 10 gtt. sat. alc. sol.
..	+	..	..	..	*2.0	0.51	74	1.630	0.563	0.815	3.196	*Killed April 23, 1907.
..	+	..	+	..	6.9	1.55	77	0.547	0.060	0.079	0.353	
..	..	..	..	+	21.1	3.38	84	0.155	0.028	0.028	0.045	
..	..	..	+	+	*72.0	13.15	82	0.610	0.083	0.008	0.054	*Left lobe removed April 1, 1907. Cretinoid dog.
..	..	..	+	..	*57.2	11.97	78	16.746	2.633	0.292	1.399	*Killed April 8, 1907. Fed iodin, 7 gtt. sat. alc. sol.
+	..	+	..	..	1.5	0.38	74	0.477	0.065	0.318	1.255	
..	..	+	..	..	3.1	0.87	72	0.569	0.084	0.183	0.654	Scabies.
..	+	..	+	..	5.82	1.34	76	0.702	0.152	0.131	0.569	
..	+	..	+	..	4.29	1.007	76	0.634	0.098	0.148	0.631	
..	..	..	+	..	16.97	3.6	79	0.608	0.115	0.035	0.169	
..	..	..	+	+	5.09	0.8	84	0.185	0.037	0.036	0.231	
..	..	..	+	..	2.5	0.65	74	0.246	0.033	0.098	0.378	
..	+	..	..	..	*14.25	3.41	76	4.249	0.334	0.298	1.246	*Left lobe removed April 17, 1907. No iodin.
..	+	..	..	..	*14.0	4.03	71	1.302	0.102	0.092	0.323	*Killed May 22, 1907.
..	..	+	..	..	*2.25	0.36	88	0.108	0.005	0.051	0.300	*Left lobe removed April 17, 1907. No iodin.
..	..	..	..	..	*2.3	0.41	82	0.954	0.332	0.415	2.326	*Killed June 5, 1907.
..	..	+	..	..	3.78	0.98	74	0.892	0.059	0.235	0.910	



	..	+	..	..	..	*14.25	3.41	76	4.249	0.334	0.298	1.246	*Left lobe removed April 17, 1907. No iodin.
	..	..	+	..	..	*14.0	4.03	71	1.302	0.102	0.092	0.323	*Killed May 22, 1907.
	..	..	+	..	..	*2.25	0.36	88	0.108	0.005	0.051	0.300	*Left lobe removed April 17, 1907. No iodin.
	..	..	+	..	..	*2.3	0.41	82	0.954	0.332	0.415	2.326	*Killed June 5, 1907.
	..	..	+	..	..	3.78	0.98	74	0.892	0.059	0.235	0.910	

[illegible]	[illegible]	1.83	Terrier. Pup	Fair	Yellow-pink	Firm	Reduced	
[illegible]	F.	1.53	Terrier. Pup	Emaciated	Yellow-pink	Firm	Reduced	
[illegible]	M.	11.3	Terrier. Middle	Good	Pink, fleshy	Soft	None	
[illegible]	M.	5.4	Collie. Pup	Good	Red, fleshy	Soft	None	
[illegible]	F.	14.5	Bull. Middle	Fair	Yellow-pink	Moderate	Reduced	
[illegible]	F.	9.07	Collie. Pup	Good	Yellow, translucent	Firm	Normal	
[illegible]	M.	5.9	Beagle. Young	Poor	Gray-pink	Moderate	Reduced	
[illegible]	M.	8.16	Terrier. Young	Good	Pink, fleshy	Moderate	Reduced	
[illegible]	M.	5.6	Terrier. Middle	Fair	Red-yellow	Moderate	Reduced	
[illegible]	M.	11.8	Spaniel. Middle	Good	Red-opaque	Soft	Reduced	
[illegible]	M.	10.0	Terrier. Middle	Good	Yellow-pink	Moderate	Reduced	
[illegible]	M.	11.9	Hound. Middle	Poor	Pink-opaque	Moderate	Reduced	
[illegible]	M.	6.3	Bull terrier. Pup	Excellent	Clear, yellow, translucent	Firm	Normal	
[illegible]	F.	6.3	Terrier. Middle	Fair	Gray, translucent	Firm	Normal	
A-40	M.	14.0	Setter. Middle	Good	Yellow-pink	Firm	Reduced	
A-41	F.	5.0	Terrier. Pup	Poor	Fleshy-pink	Soft	None	
A-42	M.	12.7	Pointer. Middle	Good	Yellow-pink	Firm	Normal	
A-43	F.	6.0	Terrier. Middle	Good	Clear, yellow, translucent	Firm	Normal	
A-44a	F.	7.7	Hound. Six months	Poor	Red, gray	Moderate	Reduced	
A-44b	F.	7.7	Hound. Six months	Poor	Red, gray	Moderate	Reduced	
A-45a	M.	6.3	Terrier. Middle	Good	Pink, opaque	Soft	None	
A-45b	M.	6.3	Terrier. Middle	Good	Pink, opaque	Soft	None	
A-46	M.	10.4	Bull. Middle	Good	Gray, translucent	Firm	None	
A-47	F.	6.3	Spaniel. Young	Good	Pink, opaque	Moderate	None	
A-48	M.	13.6	Terrier. Middle	Good	Clear, yellow, translucent	Firm	Normal	
A-49	F.	5.4	Cur. Middle	Fair	Pink, translucent	Firm	Normal	
A-50	F.	17.0	Bull. Middle	Good	Pink, translucent	Firm	Reduced	
A-51a	M.	3.2	Terrier. Middle	Fair	Pink, translucent	Moderate	Reduced	
A-51b	M.	3.0	Terrier. Middle	Emaciated	Pink, translucent	Moderate	Normal	
A-52a	F.	2.7	Terrier. Pup	Fair	Pink, opaque	Soft	None	
A-52b	F.	2.8	Terrier. Pup	Good	Clear, yellow	Firm	Normal	
A-53	F.	9.0	Spaniel. Middle	Good	Gray-pink	Moderate	Reduced	
A-54	M.	5.4	Terrier. Middle	Good	Red, opaque	Soft	None	
A-55a	M.	7.27	Bull. Pup	Poor	Purple, opaque	Soft	None	
A-55b	M.	6.36	Bull. Pup	Poor	Pink, opaque	Soft	None	
A-56	F.	7.3	Spaniel. Middle	Good	Clear, yellow	Firm	Normal	
A-57	F.	6.8	Collie. Middle	Fair	Pink-yellow	Firm	Normal	
A-58	F.	5.0	Terrier. Young	Poor	Pink, opaque	Moderate	Reduced	
A-59	F.	11.0	Collie. Old	Good	Pink translucent	Moderate	Reduced	
A-60	F.	5.3	Terrier. Young	Good	Pink, opaque	Soft	Reduced	
A-61	F.	4.9	Terrier. Young	Good	Pink, opaque	Soft	Reduced	
A-62	M.	7.3	Terrier. Middle	Good	Pink, translucent	Firm	Normal	
A-63a	F.	12.7	Spaniel. Middle	Good	Pink, translucent	Firm	Normal	
A-63b	F.	12.7	Spaniel. Middle	Good	Yellow, translucent	Firm	Normal	
A-64a	M.	2.7	Collie. Pup	Excellent	Purple opaque	Moderate	Reduced	
A-64b	M.	4.1	Collie. Pup	Excellent	Pink, translucent	Firm	Normal	
A-65	M.	15.0	Collie. Middle	Excellent	Pink, translucent	Firm	Normal	
A-66	M.	6.81	Cur. Middle	Fair	Pink, opaque	Soft	Reduced	
A-67	M.	34.5	Hound. Middle	Excellent	Red, opaque	Soft	None	
A-68	M.	5.0	Terrier. Young	Fair	Pink, opaque	Soft	Reduced	
A-69	F.	7.0	Cur. Old	Fair	Pink, opaque	Soft	None	
A-70	M.	15.9	Spaniel. Middle	Fair	Pink, opaque	Soft	Reduced	
A-71	M.	5.0	Terrier. Middle	Fair	Pink, opaque	Moderate	Reduced	
A-72	F.	7.7	Cur. Old	Fair	Gray, opaque	Soft	Reduced	
A-73a	M.	8.6	Bull. Young	Good	Red, opaque	Moderate	Reduced	
A-73b	M.	7.1	Bull. Young	Emaciated	Red, translucent	Firm	Reduced	
A-74a	F.	5.44	Dachshund. Young	Good	Pink, opaque	Moderate	Reduced	
A-74b	F.	6.35	Dachshund. Young	Good	Pink, opaque	Moderate	Reduced	
A-75	M.	6.8	Cur. Middle	Good	Clear, translucent	Firm	Abundant	
A-76	M.	5.4	Cur. Middle	Fair	Pink, opaque	Soft	None	
A-77	M.	34.0	Collie. Old	Fair	Gray, opaque	Moderate	None	
A-78	M.	9.9	Bull. Middle	Good	Pink, translucent	Moderate	Reduced	
A-79	M.	13.6	Beagle. Old	Good	Pink, opaque	Soft	None	
A-80	F.	11.7	Terrier. Middle	Good	Pink, translucent	Firm	Normal	
A-81	F.	6.2	Terrier. Middle	Excellent	Pink, translucent	Moderate	Normal	
A-82	M.	15.0	Collie. Middle	Good	Pink, translucent	Firm	Normal	
A-83	M.	11.8	Cur. Middle	Fair	Pink, translucent	Firm	Normal	
A-84	F.	12.7	Terrier. Old	Fair	Pink, translucent	Moderate	Reduced	
A-85	F.	3.3	Terrier. Middle	Fair	Pink, opaque	Moderate	None	
A-86	M.	9.0	Cur. Middle	Excellent	Clear, yellow, translucent	Firm	Normal	
A-87	F.	4.7	Cur. Young	Fair	Clear, yellow, translucent	Firm	Normal	
A-88	F.	5.0	Terrier. Young	Good	Clear, yellow, translucent	Firm	Normal	
A-89	M.	10.4	Terrier. Old	Good	Clear, yellow, translucent	Firm	Normal	
A-90	M.	5.4	Terrier. Old	Fair	Clear, pink, translucent	Firm	Abundant	
A-91	M.	10.0	Terrier. ?	Fair	Pink, translucent	Moderate	Abundant	
A-92	F.	8.2	Terrier. Middle	Fair	Pink, translucent	Moderate	Normal	
A-93	F.	7.0	Terrier. Middle	Excellent	Clear, yellow, translucent	Firm	Normal	
A-94a	F.	2.15	Terrier. Middle	Fair	Pink, translucent	Firm	Normal	
A-94b	F.	1.95	Terrier. Middle	Poor	Pink, translucent	Firm	Normal	
A-95a	F.	5.9	Cur. Middle	Fair	Red, translucent	Firm	Normal	
A-95b	F.	5.67	Cur. Middle	Fair	Pink, translucent	Firm	Normal	
A-96	F.	4.5	Terrier. Young	Good	Red, opaque	Moderate	None	
A-97	M.	6.0	Prince Charles. Young	Good	White-yellow	Hard	None	
A-98	F.	5.9	Cur. Middle	Fair	Pink, translucent	Firm	Normal	
A-99	F.	5.4	Terrier. Young	Good	Pink, opaque	Soft	None	
A-100	F.	5.9	Cur. Middle	Good	Pink, translucent	Moderate	Reduced	
A-101	M.	5.4	Cur. ?	Fair	Pink, fleshy	Soft	Reduced	
A-102	F.	3.6	Terrier. Middle	Good	Pink, fleshy	Soft	None	
A-103	M.	8.6	Spaniel. Middle	Good	Pink, translucent	Moderate	Normal	
A-104a	F.	11.8	Bull. Middle	Fair	Brown, translucent	Firm	Normal	
A-104b	F.	9.52	Bull. Middle	Fair	Brown, translucent	Firm	Normal	
A-104c	F.	9.40	Bull. Middle	Poor	Pink, translucent	Moderate	Reduced	
A-104d	F.	9.10	Bull. Middle	Poor	Pink, opaque	Moderate	None	
A-104e	F.	11.4	Bull. Middle	Good	Gray red	Firm	Reduced	
A-104f	F.	11.4	Bull. Middle	Good	Atrophic thymus			
A-104	F.	7.71	Terrier. Middle	Good	Yellow, translucent	Firm	Normal	
A-107a	F.	4.54	Cur. Young	Fair	Yellow, translucent	Firm	Normal	
A-108a	F.	4.54	Cur. Young	Fair	Yellow, translucent	Firm	Normal	
A-109a	F.	5.4	Hound. Eight months	Fair	Pink, fleshy	Soft	None	
A-110a	M.	8.5	Setter. Six months	Poor	Pink, fleshy	Soft	None	
A-111	M.	12.7	Bull terrier. Middle	Good	Yellow, translucent	Firm	Normal	
A-112	F.	5.4	Cur. Young	Good	Pink, translucent	Moderate	Reduced	
A-113	F.	5.89	Terrier. Young	Good	Yellow, translucent	Firm	Normal	

						7.2	1.4	80	0.084	0.035	0.012	0.061	
		+				8.6	2.27	74	4.676	0.351	0.543	2.060	A reverted glandular hyperplasia (spontaneous).
						*0.24	0.04	83	0.002	0.038	0.380	2.30	*Right lobe removed Feb. 15, 1907. Fed 15 gtt. sat. als. sol. iodin.
		+				*0.305	0.06	80	0.215	0.053	0.705	3.467	*Killed April 2, 1907. Had grown rapidly. Muscle—slightest trace iodin.
						*0.25	0.07	72	0.062	0.033	0.248	0.886	*Right lobe removed Feb. 15, 1907. No iodin administered.
			+			*0.15	0.025	83	0.038	0.024	0.253	1.52	*Died April 2, 1907. Pneumonia. Iodin—slightest possible trace in muscle.
					+	8.4	1.54	82	0.035	0.003	0.004	0.023	
					+	4.8	0.44	88	0.031	0.006	0.006	0.069	
		+				8.25	1.98	76	2.423	0.167	0.293	1.224	Beginning reversion.
		+		+		2.2	0.487	77	0.631	0.069	0.286	1.296	
		+		+	+	29.8	7.24	75	0.449	0.076	0.015	0.062	Probably marked glandular.
		+		+		25.0	5.75	77	1.771	0.216	0.071	0.308	Reverting, spontaneously.
				+		4.9	0.72	85	0.015	0.173	0.125	0.854	
				+		22.0	5.75	74	1.679	0.142	0.076	0.282	
		+		+		7.0	2.08	70	1.823	0.183	0.262	0.784	Reverting, spontaneously.
				+	+	40.0	11.06	72	4.015	0.305	0.100	0.303	
		+				1.3	0.31	77	0.984	0.156	0.757	3.205	
				+		1.7	0.44	74	0.108	0.017	0.063	0.243	
				+		4.5	1.184	74	0.890	0.092	0.197	0.752	
					+	5.8	0.87	85	0.046	0.009	0.008	0.053	
		+		+		6.5	1.56	76	1.271	0.100	0.195	0.815	
		+				1.25	0.115	91	0.415	0.039	0.332	3.608	
				+	+	*40.0	8.3	79	1.021	0.132	0.025	0.123	*Right lobe removed March 14, 1907. Gland hemorrhagic.
				+	+	*25.0	3.74	85	0.288	0.037	0.011	0.077	*Died, wound infection after 2 days. Half left lobe used for iodin, absolute amount.
					+	*4.0	0.75	81	0.015	0.002	0.004	0.020	*Right lobe removed, March 14, 1907.
					+	*1.1	0.24	78	0.015	0.002	0.013	0.062	*Killed, infected, March 16, 1907. Half ± l. lobe used for iodin—absolute amount.
					+	3.35	0.685	80	0.092	0.008	0.027	0.184	
					+	8.0	1.58	80	0.013	0.002	0.002	0.008	
		+				3.1	0.86	72	1.753	0.128	0.565	2.033	Considered colloid, using strict classification.
	+		+			1.7	0.54	68	0.261	0.048	0.153	0.483	
		+	+			16.1	4.69	70	2.021	0.119	0.125	0.431	Spontaneous reversion.
		+				*22.1	4.47	79	3.160	0.087	0.138	0.707	*Left lobe removed March 29, 1907. Fed desiccated thyroid (commercial).
		+				*23.1	5.85	74	5.669	1.889	0.245	0.969	*Died April 4, 1907. Pneumonia. Received 6 tablets, each 5 grains.
				+	+	*3.6	0.52	85	0.215	0.079	0.057	0.413	*Right lobe removed March 29, 1907. Fed iodin, 10 gtt. sat. alc. sol.
		+				*2.0	0.51	74	1.630	0.563	0.815	3.196	*Killed April 23, 1907.
		+		+		6.9	1.55	77	0.547	0.060	0.079	0.353	
					+	21.1	3.38	84	0.155	0.028	0.028	0.046	
				+	+	*72.0	13.15	82	0.610	0.083	0.008	0.054	*Left lobe removed April 1, 1907. Cretinoid dog.
				+		*57.2	11.97	78	16.746	2.633	0.202	1.399	*Killed April 8, 1907. Fed iodin, 7 gtt. sat. alc. sol.
	+		+			1.5	0.38	74	0.477	0.065	0.318	1.255	
			+			3.1	0.87	72	0.569	0.084	0.183	0.654	Scabies.
		+		+		5.82	1.34	76	0.702	0.152	0.131	0.569	
		+		+		4.39	1.007	76	0.634	0.098	0.148	0.631	
				+	+	16.97	3.6	79	0.808	0.115	0.035	0.169	
				+	+	5.00	0.8	84	0.185	0.037	0.036	0.231	
			+			2.5	0.65	74	0.246	0.033	0.098	0.378	
						*14.25	3.41	76	4.249	0.334	0.298	1.246	*Left lobe removed April 17, 1907. No iodin.
		+				*14.0	4.03	71	1.302	0.102	0.092	0.323	*Killed May 22, 1907.
			+			*2.25	0.36	88	0.108	0.005	0.051	0.300	*Left lobe removed April 17, 1907. No iodin.
		+				*2.3	0.41	82	0.954	0.332	0.415	2.326	*Killed June 5, 1907.
		+				3.78	0.98	74	0.892	0.059	0.235	0.910	
				+	+	9.0	2.05	77	0.346	0.059	0.038	0.169	
					+	18.7	4.34	76	0.708	0.023	0.042	0.184	
				+	+	3.25	0.66	79	0.138	0.028	0.042	0.209	
				+	+	2.75	0.53	80	0.031	0.004	0.011	0.058	
				+		10.4	2.45	76	0.977	0.061	0.004	0.399	
				+		3.6	0.786	78	0.323	0.064	0.089	0.410	
		+			+	95.0	10.29	88	2.213	0.287	0.023	0.215	Hemorrhagic-cystic complications.
				+		*2.6	0.44	83	0.185	0.021	0.071	0.420	*Left lobe removed April 25, 1907. Chorea. Five gtt. sat. alc. sol. Iodin.
						*2.1	.....	..	***	.....	.....	.....	*Died May 4, 1907. Acute distemper. ***Specimen destroyed.
				+		*3.6	0.50	86	0.261	0.048	0.072	0.521	*Left lobe removed April 25, 1907. No iodin.
		+				*2.8	0.55	80	0.799	0.125	0.275	1.452	*Killed June 1, 1907.
		+				6.4	1.69	73	2.702	0.397	0.422	1.599	Spontaneous reversion.
				+	+	6.4	1.44	77	0.222	0.041	0.034	0.154	
					+	300.0	52.38	83	2.410	0.070	0.016	0.092	Iodin calculated from left lobe. Old hemorrhages. Neoplasm.
				+		2.9	0.77	73	0.399	0.039	0.137	0.519	
					+	37.0	7.69	79	0.473	0.035	0.012	0.061	
		+				8.24	1.29	84	1.091	0.093	0.132	0.846	Spontaneous reversion. Pregnant.
		+	+			7.99	1.71	78	1.842	0.297	0.230	1.077	
		+	+			1.43	0.25	83	0.200	0.013	0.139	0.800	
		+	+			3.4	0.65	80	0.383	0.032	0.112	0.580	Iodin calculated from left lobe.
		+				3.0	0.54	82	0.400	0.031	0.133	0.741	
			+	+		2.0	0.31	84	0.138	0.042	0.069	0.445	
		+				3.2	1.02	68	3.325	0.358	1.039	3.261	
		+				1.3	0.29	78	1.384	0.294	1.064	4.772	
			+			1.5	0.25	83	0.107	0.021	0.071	0.428	
			+			2.2	0.42	84	0.664	0.063	0.302	1.443	
			+			17.1	4.27	76	6.659	1.233	0.389	2.563	
			+			67.7	16.4	75	9.124	0.912	0.134	0.538	
			+			3.5	0.65	81	0.666	0.081	0.190	1.028	Pregnant.
		+	+			3.2	0.62	80	1.538	0.218	0.480	2.480	
			+			*1.5	0.28	81	0.184	0.085	0.122	0.657	*Left lobe removed May 11, 1907. No iodin.
			+			*1.0	0.21	79	0.215	0.110	0.215	1.024	*Died May 25, 1907. Mercuric chlorid poisoning.
			+			*5.1	1.2	76	1.284	0.218	0.251	1.076	*Left lobe removed May 25, 1907. Isthmus. No iodin.
			+			*3.4	0.77	74	0.554	0.097	0.163	0.719	*Killed June 6, 1907.
				+	+	1.7	0.28	83	0.185	0.041	0.109	0.660	
			+			1.89	0.48	74	0.154	0.025	0.081	0.320	Extensive calcification of capsule—lobes very small.
		+				3.65	0.95	74	1.801	0.320	0.512	1.990	
					+	7.7	1.32	83	0.102	0.019	0.013	0.077	
			+	+		4.6	1.18	74	0.979	0.166	0.213	0.830	Reverting.
				+	+	24.0	5.15	78	1.344	0.249	0.056	0.261	
					+	5.0	0.64	87	0.077	0.021	0.015	0.120	
			+			1.3	0.22	83	0.107	0.012	0.063	0.480	
			+			*29.5	3.19	89	0.986	0.083	0.033	0.308	*Right lobe removed June 25, 1907. No iodin.
			+	+		*15.0	2.67	82	0.987	0.066	0.066	0.369	*Approximately half of left lobe removed July 15, 1907. No iodin.
			+	+		*3.0	0.49	84	0.296	0.031	0.069	0.554	*Approximately half of remaining portion of left lobe removed, Sept. 10, 1907. No iodin.
					+	*4.5	0.60	..	0.203	0.039	0.022	0.115	*Remaining portion of left lobe removed Dec. 7, 1907. No iodin.
					+	*0.95	0.23	75	0.099	0.009	0.005	0.410	*Killed Jan. 21, 1908. No trace of thyroid lobes; 2 accessory aortic thyroids. Weight 0.95 gms.; 5 gtt. syrup ferrous iodid and 6 5-gr. tablets desiccated thyroid.
						*7.6	2.49	67	0.046	0.004	0.006	0.018	*Killed Jan. 21, 1908. Spec. thymus with no visible access. thyroids.
		+				*3.5	0.70	80	1.786	0.232	0.510	2.738	*Admitted May 17, 1907. Right and half of left lobes removed Sept. 10, 1907. Between pregnancies.
		+				4.1	0.82	41	0.709	0.131	0.173	0.865	Right and half left lobes removed July 15, 1907; 12 gms. desiccated thyroid fed before operation "Spec. C." Hyperplastic.
		+				*2.1	0.34	84	0.923	0.203	0.439	2.714	*Right and half left lobes removed July 15, 1907; 11 gms. desiccated thyroid fed before operation "Spec. D." Normal.
													*Right lobe removed Oct. 30, 1907.
					+	*33.5	4.44	92	0.301	0.056	0.009	0.070	
					+	41.0	5.33	87	0.330	0.038	0.008	0.031	
		+				*47.0	12.35	73	32.480	2.557	0.691	2.630	*Fed 130 gtt. syrup ferrous iodid. Killed Jan. 15, 1908. Reversion of marked glandular.
			+	+		*4.15	0.74	82	0.246	0.072	0.078	0.332	*Left and two-thirds right lobes removed Jan. 15, 1908. Early preg.
		+	+			*4.7	0.99	79	0.507	0.086	0.108	0.513	*Left and two-thirds right lobes removed Jan. 15, 1908. Late pregnancy. Died tetany Jan. 24, 1908; aborted.

* Weights are, in most cases, abridged to a single figure to right of decimal point. This should be

nancy. Died tetany Jan. 24, 1908; aborted.

uld be noted in referring to the figures in the iodin column, for the latter were computed on the actual weights.

found in the dog. The problem of human goiter at the present time is practically one of a study of toxic (exophthalmic) goiter, since the simpler forms are easily controlled.

The investigations in the past have been largely concerned with the elaborations of methods of treatment or a discussion of the various symptoms and signs. The underlying factors of most of these signs and symptoms are either unknown to us or are common to other nervous and mental affections as well. Further advance in our knowledge as to the nature of the process from the purely clinical side is, therefore, scarcely to be expected. The first step in undertaking a systematic study of exophthalmic goiter, it seems, should be that of providing a definite, strict anatomic classification, checked in every instance by chemical and physiologic examinations of the thyroid, after which we must seek to bring the clinical observations into relation with these findings.[47]

CONCLUSIONS.

1. Iodin is necessary for normal thyroid activity.

2. Iodin is the main index to the physiologic value of the thyroid secretion (thyreoglobulin) to the body.

3. The percentage of iodin varies with the amount of colloid in the several degrees of hyperplasia; the colloid varies inversely with the degree of thyroid hyperplasia; the iodin varies inversely with the degree of thyroid hyperplasia.

4. The colloid gland (goiter) is the quiescent or normal state of a gland which has previously been a glandular hyperplasia and obeys all the biologic laws of a normal gland.

5. In the classification of thyroid changes (excluding infections and neoplasms) four major groups must be recognized, viz.: (1) normal glands, (2) colloid glands, (3) hyperplastic glands (all grades), (4) complications engrafted on any of the three preceding groups.

6. The ability of the thyroid glands to store iodin depends on the degree of glandular hyperplasia rather than on the form or mode of administration of iodin.

47. It is impossible to ascertain the anatomical condition of the gland except by histologic examinations, and in the determination of normal glands this is doubly important. It should be pointed out that in a scientific investigation there is no "normal gland for a district," as was stated by Oswald. He considered a gland non-goitrous in Switzerland if it weighed less than 95 gms. (normal adult sea coast glands average 30 to 40 gms). Our standard of normal is borrowed from the sea coast type of gland and in goitrous districts this standard is rarely attained.

7. The optimum therapeutic effects of iodin on the thyroid gland are only obtained with doses vastly smaller than those usually employed.

8. The percentage of iodin which a thyroid may contain is variable, but the minimal percentage necessary for the maintenance of normal gland structure is quite constant.

9. Commercially desiccated thyroid has a very inconstant iodin content and, therefore, has a variable physiologic activity and therapeutic value.

10. The problem of human goiter, both anatomically and chemically, should be investigated along lines similar to those adopted for the dog.

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LYMPHANGITIS AND PERILYMPHANGITIS OF THE LIVER IN THEIR RELATIONS TO THE INFLAMMATIONS OF THE ORGAN.

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The importance of the lymphatics in the inflammatory lesions of parenchymatous organs is well recognized. They are not only frequent carriers of infection, but in the absorption of inflammatory products their condition becomes a paramount issue in the ultimate fate of the organs.

We know that in pneumonia, for instance, the state of the lymphatics determines the resorption of the exudate and, therefore, the termination of the whole disease. Obliteration of the lymphatics by an acute lymphangitis and perilymphangitis retards the resolution until these paths have been cleared, and, if this does not take place, aids the termination into gangrene or abscess. Again, permanent destruction of lymphatics, as in chronic essential emphysema and in senile atrophy of the lung, are grave factors against rapid removal of inflammatory exudates and are almost entirely responsible for the long-continued, irregular course often taken by inflammations of the lungs, as well as for their frequent fatal termination in persons who already have the above-mentioned diseases. The same considerations apply with equal force to other parenchymatous organs. In the liver, however, their importance as carriers of infection and as determining factors in the course and termination of inflammatory lesions has been less emphasized than in connection with other organs—certainly much less emphasized than the rôle of the bile ducts and blood vessels, especially the vessels of the portal circulation. It is erroneous, however, to believe that the lymphatics of the liver may be disregarded or viewed as of secondary importance, for they present very definite and important changes in the various inflammatory conditions of this organ.

I shall confine myself in this article to the condition of the lymphatics in the "acute," "subacute," and "chronic" inflammations. For their study we have had unusual opportunity in this laboratory during the last few years, and some interesting cases have already been described

in their main features.[1] These cases, of which I need not repeat the details here, as well as some other typical "acute" inflammations occurring in connection with general infections, "chronic" forms, given in cirrhosis of the liver, and finally some found in acute exacerbations of "chronic" cirrhosis, furnish the basis of these observations. I shall disregard for the present specific affections, like the infective granulomata, in their relation to the lymphatics of the liver, leaving them for future consideration.

The liver, as is well known, is supplied by a rich network of lymphatics which is derived from two sources. The first and most important set, as far as the parenchyma is concerned, is that which accompanies the portal vessels, the bile ducts, the hepatic artery and the hepatic vein. The second and superficial set forms an extensive network within the capsule, and communicates with the first by means of channels through Glisson's capsule. Whether lymph channels occur within the acini is still a disputed question. From the pathological standpoint both of these lymphatic systems of the liver appear to have at least some degree of independence, for severe affections may remain confined to one without involving the other. Perhaps the best illustrations of this distinction are found in cases of Curschmann's so-called "sugar-glazed" liver, which is a hyperplastic deforming perihepatitis, or in cases of Pick's pseudocirrhosis, or in cases of polyserositis or hyaloserositis. Common to all of these is an enormous productive inflammatory thickening of the serous coat of the liver with extensive involvement of the superficial lymphatics only. On the other hand, in my experience, it is very rare to find extensive lymphatic involvement of the superficial or capsular set in inflammations of the liver itself, but these show marked disease of all internal lymphatics of a type which I shall presently describe. The only exceptions are cases in which a complicating peritonitis affects the lymphatics of the capsule.

It follows, therefore, that as far as the fate of the liver itself is concerned the affections of the internal lymphatics are the paramount issue, and I shall confine myself to them.

First, then, with regard to the so-called acute and subacute (better, exudative and productive) inflammations.[2] I shall consider these together on account of their close relationship and the similarity of the affections

1. Symmers, D.: Am. Jour. Med. Sci., 1908, cxxxv, No. 2.

2. I use these terms in Cohnheim's and Orth's sense: Cohnheim, Vorlesungen über allgemeine Pathologie, 1877, p. 281; also Orth's Lehrbuch der speziellen pathologischen Anatomie, Berlin, 1887, Preface p. 4. Others speak of proliferative instead of productive inflammations (Ziegler).

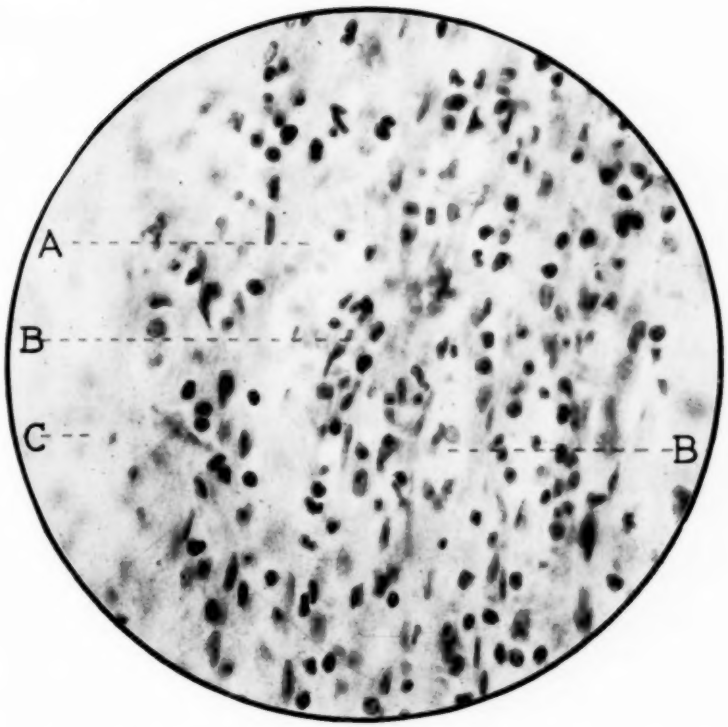

Fig. 1.—Exudative lymphangitis and perilymphangitis of a portal space (exudative interstitial inflammation of the liver); acute diffuse hepatitis. *a*. Blood vessel. *b*. Dilated lymph spaces filled with serum, leucocytes, mononuclear cells (desquamated endothelial cells.) *c*. Adjoining cloudy liver-cells. Zeiss: Oil immersion 2 mm. Ocular 4 mm.

of the lymphatics in the two. Changes occur here partly within and partly without the lymphatic channels of the interstitial tissue between the lobules. The lymphatics are generally dilated with stagnant lymph; they are filled with coagulum and large and small mononuclear cells of the lymphoid type, desquamated endothelial cells and polymorphonuclear leucocytes (Fig. 1). In some cases this condition is well marked in the initial stages of the lesion, and it may form the central feature of the inflammatory affection of the interlobular septa—an acute lymphangitis. It may be immediately recognized by the regular streaky infiltrations of the interstices following exactly the line of the lymphatic courses. More frequently an involvement of the surrounding structures follow. As a result of the blocking of the lymph stream, the perilymphatic tissue becomes edematous (Fig. 1). This leads primarily to widening of the tissue spaces around the lymphatics, and the cellular infiltration with lymphocytic cells and polymorphonuclear leucocytes extends now to these structures. It may remain confined to the tissue spaces in the immediate neighborhood of the lymphatics, or it may, especially in advancing lesions, infiltrate more or less diffusely all the interstitial tissue. In other words, the lymphangitis becomes associated with a perilymphangitis.

The anatomic distribution of the lymphatic channels in the liver, which is mainly along the paths and in the sheaths of the vessels and the bile ducts, necessarily implicates them in all affections which take their origin from or around these latter structures. Even in these cases the lymphatic involvement, although secondary, becomes of great importance in the dissemination of the inflammation, for the lymphatics will not remain locally affected, but will carry infection to other distant parts of the liver substance. This factor reserves for the lymphatics a certain independence even in those cases in which they have become secondarily affected as the result of primary biliary and vascular infections. In other words, it is not necessary that the lymphangitis and perilymphangitis progress *pari passu* with the inflammation of the ducts and the vessels; nor does the severity of the lymphatic affection stand in a constant definite ratio to that of the bile ducts or the blood vessels. The active inflammatory process of the lymphatics necessarily modifies the extension and severity of the affection in each case. It has already been mentioned that we must attach to them an important rôle in the dissemination of a lesion. On the other hand, early and complete plugging of the lymphatics would form an aid for the localization of an infection. Further—and herein lies a very essential feature—

all resorption of inflammatory products must be delayed or entirely suspended in areas thus affected, as long as the lymphatic circulation is interfered with by blocking of lymphatic and perilymphatic spaces. Whether, then, the liver is restored to its former integrity, or whether inflammatory changes will continue to spread or become permanent, depends largely on the status of the lymphatics. In order to have restitution to integrity it becomes necessary here, as in other parenchymatous organs, to have clear lymphatics. Although a morphological control is not possible, there can be no doubt that this occurs in a large number of cases in which the liver is "acutely" affected, but in a number of others, and they are the ones going on to productive inflammation and to true cirrhosis, restitution and clearing of lymphatics does not take place, but they show changes which, while they are not of the same exudative type as those previously described, are just as definite and important in their relation to the ultimate outcome of the disease. In these delayed cases of restitution, in which the progress of the disease is manifest, the changes in the lymphatics are especially characterized by endothelial proliferation of their walls. This endothelial proliferation leads not only to thickening of the wall, but gradually to obstruction of the lumen of these vessels, for endothelial cells gradually accumulate within the channel and sooner or later the lumen is entirely closed. This obliteration is considerably aided by free fibroblastic proliferation from without, which further tends to compress these lymphatic channels. The occlusion of these interstitial lymphatics goes, then, hand in hand with the formation of maturing fibrous connective tissue (Fig. 2). An interesting feature in this connection is the formation of new lymph channels along with new capillaries. Undoubtedly they serve here the same compensatory purpose that the newly-formed capillaries do, but, unfortunately, a large number of these newly-formed lymphatics suffer the same fate that many of the newly-formed blood vessels do; they are gradually squeezed out of existence in the maturing and growth of the increasing connective tissue.

These more slowly progressing changes in the lymphatics are no less important in the productive inflammations of the liver than they are in the exudative conditions. In the first place, it seems evident that a large number of cases that begin as exudative interstitial hepatitis are considerably aided in assuming an additional productive character or in becoming purely productive, by obliteration of the lymphatics; for this must necessarily interfere with the proper lymph stream and thereby with the proper nutriment of the parts, and thus with the resorption of the inflammatory products. As a consequence the parenchyma suffers severely

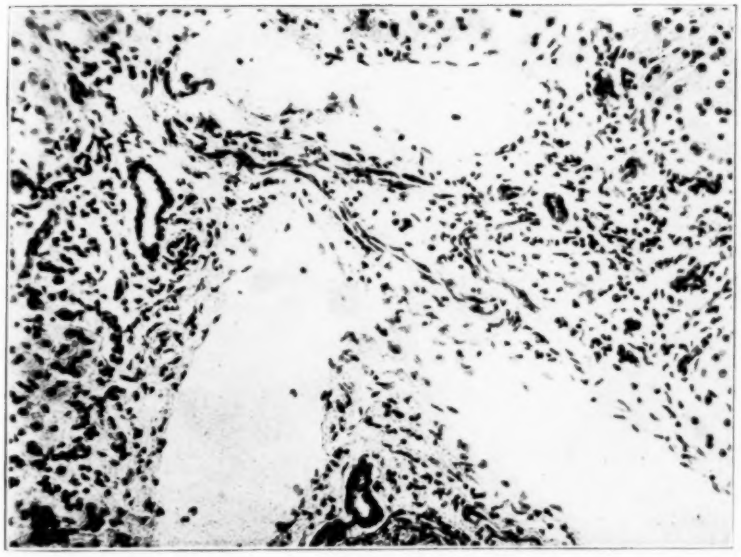

Fig. 2.—Recent productive hepatitis with productive lymphangitis around the vessels. Zeiss: Objective 16 mm. Ocular 12 mm.

and progressively; it degenerates and wastes, and favorable conditions for the production of a cirrhosis are given. Then, as fibroblastic proliferation progresses from outside, and their own endothelial proliferation from the inside, the interference with these functions becomes greater and greater, and as a result the injury to the parenchyma increases correspondingly. While an attempt is made to counteract this by the formation of new lymph channels, along with newly-formed capillaries, this is in all probability not sufficient, and in the majority of cases these newly-formed lymphatics are not even permanent, but are lost by the slow but constantly progressing inflammatory production of new tissue.

To recapitulate: Inflammatory conditions of the liver are associated with an exudative lymphangitis and perilymphangitis. If, in the subsidence of the inflammatory irritation, the lymphatics are cleared and nothing stands in the way of resorption of inflammatory irritants and products, a change to the normal may take place. If, on the other hand, the lymphatics are not cleared, they form an essential factor in the establishment of a progressing inflammation in the form of an exudative and productive or pure "cirrhosis" of the liver.

Viewed in this light, some forms of cirrhosis of the liver appear primarily only as an inflammation of the portal spaces, which, on account of unfavorable conditions, particularly for resorption, and a consequent interference with nutrition, lead to degeneration and loss of parenchyma. This is necessarily followed by a fibroblastic proliferation which replaces wasted areas. Maturing in the more slowly progressing forms, this inflammation is apt to undergo frequent exudative exacerbations. These will involve the lymphatics in exactly the same fashion as in a previously normal liver, and they will, therefore, become diffuse and lead to further injury of the parenchyma. In a liver already much changed such acute exacerbations are apt to lead to speedy exitus.

I said before that I believe that *some* forms of cirrhosis have this pathogenesis, for I do not want to imply that *all* are the result of such changes. On the contrary, there are undoubtedly forms which commence with marked injury to the parenchyma as well, and in those a hyperplastic proliferation of the connective tissue seems to follow more closely in the path of this primary, parenchymatous destruction. Histologically these two forms present distinctions. The first group includes all those cases in which, especially early in the disease, the parenchyma appears relatively well preserved, and the inflammation and formation of fibrous tissue appear almost out of proportion to the degeneration of the parenchyma. In the second group, however, are all cases in which the

parenchyma shows, even early, an extensive parenchymatous and fatty degeneration, bile imbibition and various forms of cytolysis. There the inflammatory interstitial changes are irregular, not so distinctly periinsular, but diffuse, plainly intralobular, and this diffuse infiltration which allows free invasion of inflammatory products is made possible by primary, severe involvement of the liver cells themselves. In this connection I should draw attention to the fact that the classification of the various forms of cirrhosis of the liver, which has been especially attempted by the French and to a large extent followed in this country, appears perfectly impossible from an anatomical standpoint, for these forms appear of such close relation, and merge so freely into one another, that it seems unjustifiable to attempt to hold the cirrhoses too rigidly into definite classes. We should rather view them as of a uniform nature modified only by the number and quality of surrounding conditions in each case.

One great mistake which has frequently been made, even by pathologic anatomists, the distinction of two great groups of cirrhoses, namely, the so-called interlobular and intralobular forms, is certainly based on false interpretation. As a matter of fact, all forms of cirrhosis are intralobular, for there is no cirrhosis, not even the old typical Laennec's cirrhosis, which is not intralobular. The pictures in this form of cirrhosis which have been wrongly interpreted as being the result of a distinctly interlobular formation of fibrous tissue do not in reality present such a process. They are produced only by the slow advance of bands of mature fibrous tissue into the liver parenchyma whereby groups of liver cells are cut off from their surroundings and appear in the form of islands, which have been wrongly interpreted by some writers as representing always individual lobules or groups of lobules. More correctly, these islands are frequently produced by cutting off various portions of a number of acini by a distinctly intraacinar growth of fibrous connective tissue. The distinction between this form of cirrhosis, then, and the so-called intralobular form lies not in a characteristic typical distribution of connective tissue, for in both of them this is an intralobular growth; it depends rather on the surrounding conditions of each case, which in the one limit its growth by better parenchymatous preservation, while in the other the growth is diffuse from the start on account of the greater injury to the parenchyma. Whatever other features may become associated with any case, they are not characteristic of particular groups of cirrhotic processes, but are determined by the accompanying conditions of each

case. These are mainly angiocholitis, bile duct formation, and lesions leading to stasis and ascites.

The terms interlobular and intralobular, as distinctive features of types of cirrhosis, are, therefore, false, and for descriptive purpose the terms periinsular and diffuse would be decidedly preferable. Undoubtedly combinations of the two classes are not infrequent, and this is especially well shown in cases of old periinsular cirrhosis which undergo exudative exacerbation. Here observation proves, in addition to the old mature periinsular cirrhosis, the recent more diffuse spread of inflammatory products. This may be interpreted as being due to the result of the previous interstitial inflammation, as I outlined it above, which has injured the remaining cells sufficiently to allow a free entrance of the inflammation into the remaining islands whenever an exudative exacerbation occurs. All "acute" exacerbations, then, of chronic cirrhosis lead to the so-called "mixed forms," that is, to a very diffuse distribution of the newly-formed fibrous tissue, which must, necessarily, be associated with more complicating secondary results than the limited old form upon which it was implanted.

In the discussion of the pathogenesis of cirrhosis of the liver we have, as is well known, two opposing views. Some regard it as a primary inflammatory interstitial growth and consider that the loss of parenchyma is dependent upon it. Others, however, deny the possibility of this extensive connective tissue proliferation without previous injury and waste of parenchyma, and believe the fibrous tissue growth to be an entirely compensatory process.

I am inclined to take a stand somewhat between these two, and more or less reconciling them, inasmuch as I believe that the origin of the true cirrhosis of the liver must be looked for in the interstitial inflammation; and that either this may be associated from the start with a severe injury to the parenchyma, which involves diffuse, irregular, fibrous tissue growth throughout the liver, or the parenchyma may become involved much more gradually and largely secondarily on account of the previously outlined progressive features of this interstitial inflammation. In such instances the parenchyma wastes more slowly, as a consequence of which the connective tissue grows in a more or less periinsular fashion. While, then, the origin of the cirrhosis is primarily an interstitial inflammation, the cirrhotic process proper is eminently a compensatory process which depends upon extensive or more slowly progressing, irregular destruction of the parenchyma. A combination of the two types is possible and not at all infrequent.

I can not leave this subject without a few remarks about the so-called hypertrophic cirrhosis, or Hanot's type. A proper discussion of this lesion, which, as some insist, is a distinct anatomic and clinical entity, is made extremely difficult by the conflicting testimony of its own advocates. The characteristic features of this so-called entity have been variously described, either more grossly as hypertrophy or, better, as enlargement of the liver with a smooth surface and jaundice, a large spleen and no ascites, or, microscopically, as an exclusively intralobular formation of thin connective tissue fibrils between individual liver cells around the bile ducts, with cholangitis and new bile-duct formation, and finally preservation of liver cells. Some would regard one or the other, or several of these, as the distinguishing features, and dispute the others, and few agree even with Hanot himself about the character of the process. This disagreement of authors has gone so far that a few now proclaim that the intralobular formation of delicate fibrous connective tissue, which is by every one practically admitted to occur in this disease, was not a feature of the original findings of Hanot.

Cases of cirrhoses with more or less smooth enlargement of the organ were observed from time to time before Hanot, and Hanot himself has drawn attention to these in several of his writings on the subject. Notable among them is the one by Hayem,[3] 1874. But it was Hanot who primarily insisted on the establishment of a special type on the basis of some cases which he had collected and presented in 1876. He founded his description on a number of partly anatomic and partly clinical peculiarities, which, in order to avoid confusion, I will quote in his own words found on page 89 from the original publication:[4]

It is, therefore, clear that Hanot recognized from the start an intralobular as well as an interlobular connective tissue growth without contraction, and also a catarrhal condition of the bile ducts with their abnormal development. His clinical characteristics need not detain us here, but it is interesting to know that he distinctly contrasted the pathogenesis of atrophic and hypertrophic cirrhosis, inasmuch as he was led to believe

3. Hayem: Contribution a l'etude de l'hepatite interstitielle chronique avec hypertrophie (sclérose ou cirrhose hypertrophique du foie). Arch. de physiol., 1874, i.

4. Hanot, V: Etude sur une forme de cirrhose hypertrophique du foie (cirrhose hypertrophique avec ictere chronique), Paris, 1876.

Parmi les différentes lésions du foie qui ont été englobées sous la dénomination de cirrhose hypertrophique, il en est une qui est vraiment spéciale, et qui se compose des éléments suivants: sclérose extra-lobulaire trés-accusée et sans tendance á la rétraction du tissu conjunctif de nouvelle formation; souvent aussi sclérose intro-lobulaire; developpement anormal et catharre chronique des canalicules biliaires.

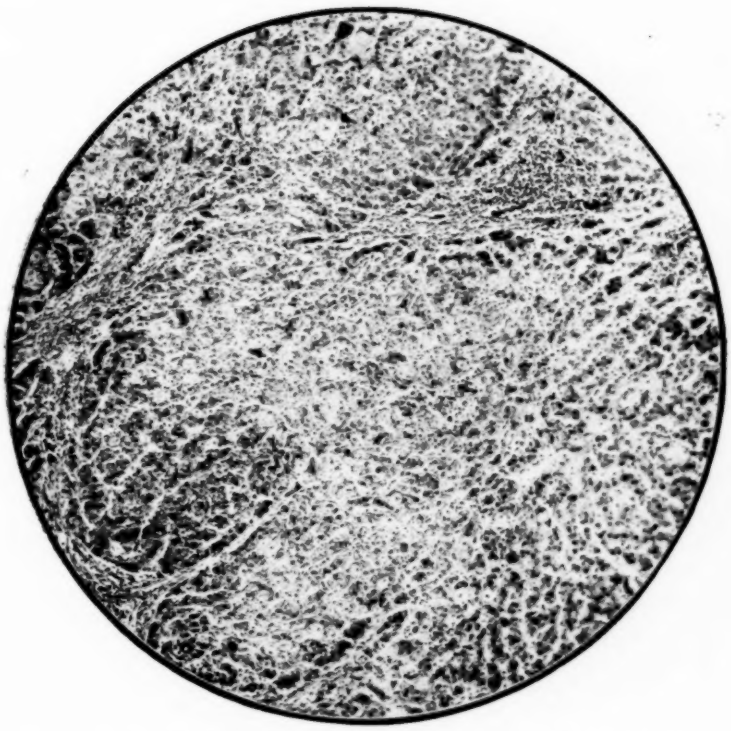

Fig. 3.—Periinsular and diffuse sclerosis; exudative and productive hepatitis, from a large but distinctly granular and much jaundiced liver. It shows a variety of lesions: In the center the type is that described by Kretz; at the periphery more a simple periinsular sclerosis. Bile-duct formation and angiocholitis moderate and irregular. Zeiss: Objective 16 mm., ocular 6 mm. The photographs are by Mr. A. J. Martin, artist to the Russell Sage Institute.

that the atrophic cirrhosis took its origin around the radicles of the portal vein, while it was characteristic of the hypertrophic cirrhosis with icterus that it took origin from the bile canaliculæ. In his later monograph on the subject[5] he also emphasizes the good preservation of the liver cells.

In the subsequent discussion of the disease, however, all of these various features which Hanot advanced then, and later in modified form, have been put forward as characteristic by its supporters, notably in order to save the disease from being disregarded as an entity. At present there are a number of different conceptions which are more or less removed from Hanot's ideas, but which still go under the name of Hanot's cirrhosis, all the distinguishing features which were originally and subsequently claimed for this disease having gradually been denied, differently interpreted or found in other forms of cirrhosis.

Hanot, as we have seen, speaks of an interlobular and intralobular cirrhosis, but he himself attached much greater significance to the bile ducts and the origin of the disease from them than to the cirrhotic lesion itself. Subsequent investigators, however, have paid more attention to the distribution of the connective tissue, and have even gone so far as to disregard the involvement of the bile ducts or the origin of the lesion from them, which was particularly emphasized by Hanot. This is especially true of some of the German writers who have accepted the division of cirrhosis into the atrophic and hypertrophic forms. Kaufman,[6] for example, claims as characteristic of Hanot's cirrhosis an extremely fine, diffuse intraacinar connective tissue proliferation, and distinguishes it distinctly from biliary cirrhosis. He further differs from Hanot in stating that the liver cells, that are definitely involved, contain fat and bile pigment, become atrophic and disintegrate with the formation of clumps of bile. He refutes the idea of good preservation of liver cells in hypertrophic cirrhosis as a false interpretation of attempts at regeneration, the latter having been demonstrated through the finding of karyokinetic figures by Prus. Very similar are the ideas, with regard to hypertrophic cirrhosis, which are held by Kretz,[7] who presented two livers before the German Pathological Society in 1905, which he considered typical of Hanot's disease. These cases were characterized by a diffuse intralobular formation of fibrous tissue with considerable atrophy of liver cells, vacuolization, and fatty infiltration, but without capillary

5. Hanot, V: La cirrhose hypertrophique avec ictére chronique, Paris, 1892.

6. Kaufman, E: Lehrbuch der speziellen pathologischen Anatomie, 1907.

7. Kretz, R.: Ueber die Abgrenzung der Hanotischen Krankeit gegen die Lebercirrhose mit Ikterus. Verhandlungen der deutschen pathologischen Gesellschaft, 1905.

cholangitis, bile imbibition, or bile thrombi. He, therefore, claims as the distinguishing feature of Hanot's cirrhosis, diffuse intralobular connective tissue growth without capillary cholangitis. It is perfectly clear from the foregoing that, while Kretz speaks of these as Hanot's cirrhosis, this cirrhotic process has not much in common with the ideas which were advanced by Hanot, since the latter paid particular attention to the involvement of the bile ducts and the good preservation of the liver cells. While, then, some of the Germans consider that Hanot's cirrhosis consists of diffuse smooth enlargement of the liver with considerable bile imbibition but no capillary cholangitis, and with a destruction of the liver cells, others follow Charcot and proclaim this a special feature. Rolleston[8] has retained more or less the original typical Hanot description and groups it as biliary hypertrophic cirrhosis.

On the other hand, some pathologic anatomists refuse to recognize any of these features as sufficiently characteristic evidence to permit of the establishment of a definite classification, and with these I must agree. In the first place it has been held that it is characteristic of the so-called hypertrophic cirrhosis to show a lack of contraction due to an even distribution of the cirrhosis, but that this may be found in other varieties of cirrhosis has long been well known. In fact Orth, in his text-book of special pathologic anatomy,[9] describes distinctly cases of smooth atrophic cirrhosis which are due to a very fine uniform distribution of the connective tissue. We have in our collection in this institute a perfect example of such a cirrhosis, which presents a smooth surface as the result of very general and even connective tissue growth which goes hand in hand with a corresponding loss of hepatic substance. On the other hand, there occur cases of cirrhosis with jaundice and marked enlargement of the organ which are distinctly granular as a whole, or in places. How are these to be regarded? The integrity of the liver cells which has been proclaimed as distinctive by some writers can not be held to be in any way characteristic. That feature is open to too much variation, and in every cirrhosis, especially in the typical atrophic forms, one will run across many areas of parenchyma which appear well preserved, to say nothing of the attempts at regeneration which have been shown by Prus. Again, in the forms with marked enlargement and jaundice the parenchyma may be diffusely and severely altered.

With regard to the distribution of the cirrhotic tissue itself, I have already stated that all cirrhoses are intralobular as well as interlobular,

8. Rolleston, H. D.: Disease of the Liver, 1905.

9. Orth, J.: Lehrbuch der speziellen pathologischen Anatomie, 1887, i.

and that a periinsular cirrhosis may at any time become a diffuse intralobular form, if in the course of exacerbations the remaining islands should become injured to such an extent as to allow of an invasion of connective tissue in the form of denser or fine fibrillar bands into them. Finally, the presence of cholangitis and bile duct formation can certainly not be characteristic, for these occur in a number of cases of ordinary cirrhosis, and, as the observations of Kretz show, they may even be absent in cases which otherwise entirely resemble Hanot's cirrhosis. It will, therefore, be seen that the conditions which may be associated with smooth or granular enlargement of the liver and with jaundice are variable and depend upon even more different conditions than were found by the originator of the term. The absence or presence of accessory conditions, like jaundice, ascites and splenic enlargement, can certainly not be utilized in the classification of the cirrhotic lesion, for they depend, as I have outlined above, upon a number of extremely variable pathological lesions which are partly the result of the cirrhotic process itself, and partly of superadded, concomitant, and more or less independent lesions.

At this present stage of our knowledge it seems unjustifiable to insist on the establishment of definite classes of cirrhoses of the liver. We have to deal here with variations which allow such frequent combinations that even clinically we can not gain much by attempting to do this (Fig. 3).

At the symposium on nephritis before the German Pathological Society in 1905 Orth made this remark at the end of the excellent presentations of Ponfick and Fr. Müller on the subject:

Die Lehre von der Nephritis enthält so viele Einzelfragen, dass wir tagelang diskutieren könnten, wenn wir sie alle eigehend behandeln wollten, ich werde mich deshalb nur auf einige kurze Bemerkungen beschänken. Es ist vorher die Hoffnung ausgesprochen worden, dass man heute festere Grundlagen für die Nomenklatur und Systematik der Nierenkrankheiten gewinnen würde, ich glaube nicht der einzige zu sein, welcher das Gefühl einer Enttäuschung empfunden hat, denn wenn man das Resultat von Referat und Korreferat übersieht, so muss man doch sagen, das dasselbe nur ist, dass wir noch fast nichts wissen.

The same sentiments I voice to-day in another subject after a review of our knowledge and some independent study of the inflammations of the liver. Those who believe that morphological investigation of diseases of organs has reached its final results should appreciate that we have really just begun to correlate our morphological experience and develop the variations in its relations. In the future, as in the past, no proper idea of a disease will exist without knowledge of these relations, and both the pathologist and the clinician of to-day should appreciate that proper conception of a disease can stand only on this basis. In the gradual evo-

lution of pathological conceptions a great many previously established sharp lines of demarcation are wiped away, just as they gradually disappeared in zoology after the appreciation of the theory of evolution.

Guided by these considerations, I now use the following very broad classification for diffuse inflammations of the liver, which, although it does not draw rigid lines, allows of the combination of variations which are much closer to the actual anatomical finding.

I have discarded entirely the terms acute, subacute and chronic, which have no place in anatomic terminology, and have substituted descriptive terms which allow proper anatomical conceptions.

1. I speak of degenerative exudative hepatitis, now called acute hepatitis, in cases which are characterized in varying degrees and in varying combinations by cellular exudation taking origin from the portal spaces, by lymphangitis, perilymphangitis and cholangitis, by diffuse parenchymatous and fatty degenerations of the liver cells, and by cytolysis and bile imbibition.

2. I speak of degenerative productive hepatitis in cases which are now grouped as subacute hepatitis, and divide them into two forms: the first with a more rapid loss of substance, grossly appears more or less granular, the second with a much more gradual loss of substance has consequently a more uniform, even distribution of connective tissue and is, therefore, smooth. Both of these may be associated with either enlargement or diminution in size of the liver. They are characterized, microscopically, by a productive cellular inflammation proceeding from the portal spaces, which is periinsular and diffuse: a productive lymphangitis and a productive pericholangitis. It is further characterized in varying degree, and more or less accentuated by, more slowly progressing, irregular, parenchymatous and fatty degenerations and fatty infiltration, cytolysis, bile imbition, and the formation of new, mature and embryonic liver cells (bile ducts).

3. I speak of productive hepatitis, for which I also use the term sclerosis of the liver (which is to be preferred to cirrhosis of the liver), and this is characterized essentially by the formation of mature, periinsular, or diffuse connective tissue formation; depending upon the loss of liver substance and the distribution of connective tissue, it is either granular or smooth and goes along with enlargement or diminution in size of the organ. It further presents very slowly progressing, irregular, parenchymatous and fatty degenerations, and fatty infiltration, cystolysis, little or moderate bile imbibition, and the formation of mature and embryonic liver cells (bile ducts).

30 West Forty-fourth Street.

RECENT ADVANCES IN OUR KNOWLEDGE OF THE UNDERLYING CHEMICAL PRINCIPLES OF DIABETIC ACIDOSIS.

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The literature pertaining to acidosis, with especial regard to its bearing on diabetes, has grown in the past few years to such dimensions that it is practically impossible for the general practitioner to keep fully abreast of the recent researches along this line. In reviewing the various articles pertaining to diabetic coma and its underlying condition, acid intoxication, it seems that since 1900 the work has taken on a distinctly new and decidedly more interesting and valuable aspect, mainly due to the energy of German investigators. While most of the work has had to do with the theoretical and experimental side, yet for a thorough understanding of the subject it is absolutely essential that the busy practitioner, not interested generally in chemical research, should be acquainted with the more recent advances in this subject. It has seemed, therefore, fitting to compile reports of recent date, to review the most important papers in detail, to summarize results, and to put these results in a paper of sufficient brevity to acquaint the average physician with the present status of diabetic acidosis.

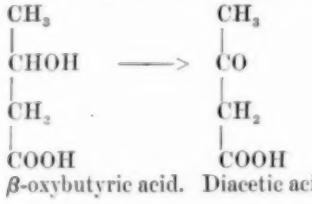
I have chosen, therefore, to limit this paper to a review of reports published from 1900 to the present time, for it is during this period that the most marked advances are seen. For a short history of the subject the reader is referred to Folin's article,[1] in which he concisely summarizes the history of the acid intoxication theory from the time of Boussingault. This part of the question will be omitted, and this paper will be confined solely to the subject of acidosis, with report of the work done on the origin of the acetone bodies, and the probable nature of the effects exerted on the animal organism by their presence. As much technical phraseology will be omitted as is concomitant with a clear representation of the subject, and the endeavor will be made to explain such chemical technicalities as can not well be avoided. I have often observed that, whereas the average practitioner speaks glibly of acidosis, oxybutyric acid, diacetic acid and aceton, he has not the slightest conception of exactly what is meant by these names, but is rather like the

1. The Jour. Am. Med. Assn., 1907, xlix, 128.

Harvard student who, on being asked his definition of "word," replied that it was "a funny sound that means something."

Butyric acid and acetic acid belong to the same group, the type of which is $C_nH_{2n}O_2$. If there is one atom of carbon, there must be two atoms of hydrogen; if two carbon atoms, there must be four hydrogen atoms, and, no matter how many carbon atoms we have in the molecule, the hydrogen atoms are twice as many, while in each molecule there are never more than two oxygen atoms. Acids formed in this way are called fatty, because their higher members occur in the natural fats, and if $C_nH_{2n}O_2$ is remembered a series of fatty acids can be theoretically formed *ad libitum*. Starting, however, with the lowest fatty acid of the series, which must of necessity have but one carbon atom, we find CH_2O_2—H.COOH—or formic acid. The two oxygen atoms, one of the carbon and one of the hydrogen atoms, are always in the combination of COOH, which is called a carboxyl radical. The next acid in series must have the formula, $C_2H_{2x_2}O_2$ in which the $N = 2$ and we have $C_2H_4O_2$,—CH_3.COOH or acetic acid. The next higher will be $C_3H_6O_2$,—CH_3.CH_2.COOH, proprionic acid, and the next above $C_4H_8O_2$—CH_3.CH_2CH_2.COOH or butyric acid. Each division of these molecules is named according to its relation in the molecule to the fundamental unchanging carboxyl group. The one nearest to the carboxyl radical is said to be in the alpha position, *a*, and one on the left of the alpha β, and the other γ.

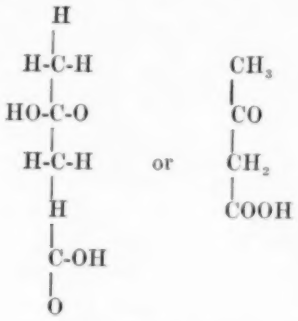
If, by a process of oxidation, there is an oxygen atom inserted in any one of the *a*, β or γ groups, we have formed an oxyacid, and if this oxidation happens to take place in the β position we have formed a β oxyacid, and if butyric acid is so oxidized β oxybutyric acid, CH_3.CHOH.CH_2.COOH. Supposing, however, the oxidation does not stop here, but that combustion continues. It has been found by chemists that the oxidation of the fatty acids in the body takes place usually in the β position, furthermore that successive oxidation takes place in the same position; in other words, the substance that is burned up by oxidation in the beta position continues to be oxidized in the same position. Accepting this as a fact, we see the following results:



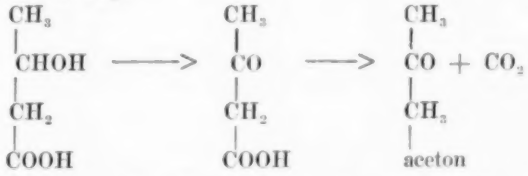
β-oxybutyric acid. Diacetic acid

in which the new body has been formed by deprivation of β-oxybutyric acid of two atoms of H, with the formation of water.

On comparing this newly formed acid with acetic acid, CH_3—COOH, we find it to be made up of two molecules of the latter, minus one molecule of water, thus:



If oxidation continues, and there is still further splitting off, we can imagine the following to take place, the new product arising by liberation of carbon dioxid CO_2:



Aceton is also called dimethylketon, the CH_3 group being called methyl, and if in a molecule the various components are held together with CO, the body is called a keton.

If normally by our qualitative tests we can detect no aceton in a specimen of urine, and we find it in a diabetic case, the organism's power to burn up the aceton is impaired, and it appears as a danger signal referable to some disturbance of metabolism. In such a case, where no diacetic acid is detected, the organism is still sufficiently able to oxidize material past oxybutyric acid, over diacetic acid, but can go no further than aceton. If, however, we find diacetic acid, there is grave disturbance, as the body has now lost the power to oxidize even this, and in such cases oxybutyric acid will generally be found, showing that marked metabolic disorders are present in the organism.

The above is stated merely to review fundamentals concerned in the chemistry of acidosis and is not to be considered as actually taking

place, though such may be the case. With this elementary chemical preface understood, there will be a clearer idea of just what is meant by β-oxybutyric acid, diacetic acid and aceton, and it will probably make more intelligible to the average physician why he dreads the appearance of diacetic acid more than of aceton.

I. ORIGIN OF ACETON BODIES.

A. *From Protein.*—Schwarz[2] thinks that aceton is not derived from proteid, as in a diabetic, during nine days of carbohydrate fasting, there were 27 grams more aceton excreted than in a period of carbohydrate diet, and the nitrogen output was no higher in the first period than in the second, which would be the case if the protein tissue were being broken down. He thinks that aceton is an expression of increased fat destruction, as it is seen when the organism has to provide heat for itself, as in carbohydrate abstinence and in hunger. Blumenthal and Neuberg[3] state that Guckelberger and Cohn had obtained aceton from casein, and to study the question of origin of aceton from proteid they investigated the action of iron salts on gelatin, and, finding that aceton was produced, they proposed the hypothesis that the iron in the body has some effect on oxidation and probably plays a rôle in the formation of aceton. Schwarz,[4] shortly after this, criticized the work of Blumenthal and Neuberg, his main objection being that they should have demonstrated β-oxybutyric acid, and if aceton is found it must be obtained by oxidation of the former. He also states that Blumenthal and Neuberg have not shown anything new, as Cotton, in 1899, had obtained aceton from gelatin, fibrin and casein by distilling with hydrogen peroxid.

Orgler[5] produced aceton from crystallized egg albumin. Neuberg and Blumenthal[6] think that aceton may be formed from all three foods —protein, carbohydrates and fats—that the last does not account for all the aceton, and they believe that it is formed from protein tissue. Their later work is merely a confirmation of their former paper.[3] Baer[7] seems to hold the view that aceton is not formed from albumin, for so long as the animal remains in nitrogen equilibrium there is no increase of aceton, but, when this is disturbed, symptoms of acidosis appear. Satta,[8]

2. Centralbl. f. Stoffwechsel-u. Verdauungskr., 1900, p. 2.
3. Deutsch. med. Wchnschr., 1901, p. 6.
4. Id., 251.
5. Hofmeister's Beitr., 1901-2, i, 583.
6. Id., 1902, ii, p. 238.
7. Arch. f. exper. Path. u. Pharmakol., 1903-4, li, 271.
8. Hofmeister's Beitr., 1904-5, vi, pp. 1 and 388.

in studying the condition of aceton formation, does not believe much in its origin from protein for the following reasons:

(*a*) There is no relation between nitrogen and aceton output.

(*b*) In diabetics, nitrogen equilibrium, even a storing up of nitrogen, can be obtained without any decrease in the excretion of aceton bodies being seen.

(*c*) Mangus Levy found that in one case 262 grams of protein was used up in three days, and 342 grams of β-oxybutyric acid were excreted, which is more than could be accounted for by supposing its origin to have been from albumin.

(*d*) The objection that a proportion between nitrogen decomposition and aceton excretion can not be made because the breaking down of the protein molecule does not go to the end products, is contradicted by the relation between sulphur and phosphorus. It has been found that there is a constant ratio between these two, but none between aceton and sulphur.

(*e*) Rosenfeld, Hirshfeld and others have reported that much albumin ingestion cuts down acetonuria.

(*f*) It is very difficult to understand why small amounts of carbohydrates, which only inhibit the albumin decomposition to a slight extent, should cause pronounced disappearance of aceton.

Satta regards it as proved that the greater amount of aceton does not come from albumin. He remarks that the mere fact of having obtained aceton outside the body by the use of strong oxidizing agents has not much value, because the amount of aceton is small, no other substance beside aceton is obtained, and because a similar procedure in the organism is not possible. Satta suggests that the aceton-forming bodies be classified as ketoplastic and antiketoplastic. The first contains those bodies which are regarded as the immediate sources of fatty acid aceton, and the second are inhibiting stuffs which prevent the formation of aceton or from which no aceton is formed (carbohydrates).

Borchardt[9] investigated the action of monamido acids on the aceton output, and, knowing that protamins and histons contain but traces of monamido acids, egg albumin a moderate amount, albumin of pancreas much, and casein a great deal, it would be expected that protamins and histons would have no antiketoplastic action, the action of the others being dependent on the amount of the monamido acids present in the molecule. At present, aceton formation is supposed to be from fat which contains ketoplastic groups—fatty acids—and antiketoplastic groups—glycerin. As the antiketoplastic group can be removed

9. Arch. f. exper. Path. u. Pharmakol., 1905, liii, 388.

from the protein molecule, the question naturally arises, Has the protein molecule, groups from which aceton bodies can be formed? If so, then those proteins which contain no antiketoplastic groups, as protamin and histons, should give an increased amount of aceton. For those proteins which contain only a moderate amount of inhibiting stuffs the result is not known, as the unknown ketoplastic and not wholly known antiketoplastic groups (leucin and monamido acids) are antagonistic, and it is not known which is the more powerful. But it is to be expected here that egg albumin poor in monamido acids has rather a ketoplastic action than the leucin-rich casein, whereas the proteid of the pancreas, corresponding to its leucin percentage, stands between both.

Borchardt states that Magnus Levy[11] found such quantities of oxybutyric acid in the urine of cases of severe diabetes, that its origin from protein or fat bodies did not account for it, and another source of aceton must be sought. The breakdown of high fatty acids to bodies with two or three carbon atoms (Magnus Levy) to form aceton is from a chemical standpoint improbable, but can be neither proved nor controverted. Borchardt used carp's eggs which contain 81 per cent. of nucleic protamin, calf's thymus containing 70 per cent. of nucleic histon, native and coagulated egg albumin, pancreas and nutrose, and found that feeding on protamin, histon and egg albumin caused a marked increase of aceton output, after pancreas he was uncertain, and with casein the aceton was diminished. His results do not correspond with Lüthje's[12] experiment on diabetics.

Lüthje found after nutrose that the nitrogen, sugar and aceton were increased, but with thymus all sank, giving as an explanation that nutrose is burned up rapidly in the organism and consequently there is a high nitrogen output, its carbohydrate-forming groups are very great, and in diabetes this causes more sugar, and, as the unused carbohydrate formers do not act antiketoplastically, the aceton is increased. Calf's thymus is more slowly used up, hence a diminution of nitrogen, and, as it contains no carbohydrate-forming groups, there is no sugar produced, and this would account for increase of aceton. The sinking of aceton means that casein contains antiketoplastic substances (carbohydrate formers), which, being stored up, are broken down in the after period and act during the period of thymus feeding as inhibiting stuffs. v. Noorden found that the different albumin bodies acted differently on the excretion of aceton, the vegetable protein having less ketoplastic

11. Quoted by Borchardt.
12. Ztschr. f. klin. Med., xxxix.

power than egg albumin. Borchardt found that when nutrose was substituted by three eggs the aceton increased, and this effect was more pronounced with 200 grams of meat.

Owing to our lack of knowledge of the split products of albuminous breakdown, the meaning of these experiments is obscure. The fact that the protein bodies which are rich in carbohydrate producers (casein, pancreas) have no ketoplastic action, is in favor of the view that the carbohydrate-forming groups of the protein molecule are inhibiting stuffs; together with these antiketoplastic groups there is a ketoplastic group. Better known than the mother substances of aceton are the antiketoplastic substances—carbohydrates, glycerin, lactic acid, and, according to Borchardt's experiments, probably a group in the protein molecule.

As stated above, Magnus Levy found that no one group (neither fat nor proteid) could be regarded as being the mother substance of aceton. Of course, the fatty acids are now known positively to be a source of aceton, but it is not known what other substances have the same property, but Borchardt believes that there is a ketoplastic group in albumin. The percentage of monamido acids in protamin, histon, egg albumin, pancreas and casein is lowest in the order of substances named, as are also the carbohydrate-forming groups, whereas the ketoplastic power increases from casein up to protamin. Protamin, histon and egg albumin increase the aceton output, the pancreas has no influence, and casein acts antiketoplastically.

Borchardt gives another explanation, however. During pepsin and trypsin digestion, protein is broken down to so-called antigroups, very resistant in nature, and to hemigroups, very readily broken up further. The first are forerunners of polypeptids and are ketoplastic; the latter are antiketoplastic. Casein is rich in hemigroups and consequently is easily broken down; whereas protamin is hardly digested by trypsin at all, and only exceptionally is broken down to proton. This theory means more than that the antigroup contains certain monamido acids, as leucin, for other amido acids, as glykopoll, belong exclusively to the antigroup. The different action of the same monamido acid in the hemi- and antigroups can be explained by supposing different union in the proteid molecule.

Which of the theories is correct has not been decided, but it is certain that the protein molecule contains ketoplastic and antiketoplastic groups, and that the proportion of one to the other determines its influence in aceton excretion.

In favor of albumin as a source of aceton, Baumgarten and Popper[13] report that aceton was a constant accompaniment of extrauterine pregnancy with hemorrhage into the peritoneal cavity. Based on this clinical observation they believe that aceton is derived from the proteid tissue in blood.

In discussing the ketoplastic and antiketoplastic bodies, Halpern and Landau[14] suggest that the antiketoplastic bodies prevent the formation of aceton by setting oxygen free during their breaking down, and that by this means aceton is oxidized. For instance, if the body, for any reason, can not use up carbohydrates, there is an increased output of aceton bodies through the lungs and kidneys, the amount depending on the degree of disturbance. Borchardt is quoted by them as saying that the antiketoplastic action depends on the amount of amido acids contained in the protein molecule, for leucin and alanin do not cause increase of aceton. Therefore, the more amido bodies the protein molecule contains, the greater its antiketoplastic property. This view of Halpern and Landau does not seem to the writer tenable, as carbohydrates, which contain no amido groups, are the most powerful of the antiketoplastic bodies.

Later, in 1907, Borchardt and Lange[15] set about to answer three questions: (1) Which components of fat and albumin act as augmentors and which act as inhibitors of aceton? (2) Are the substances which increase aceton output those from which oxybutyric acid or aceton can be derived directly? (3) Which substances are the direct source of aceton? I shall here refer only to these problems in their bearing on the question of aceton formation from protein.

Does the protein molecule contain augmenting or inhibiting aceton factors? Borchardt affirms this, but without going into the nature of these substances. At that time it was thought that monamido acids inhibit aceton output, because protein poor in monamido acids increase aceton, and *vice versa*. The question is now, What chemical substances (referring only to fatty acids and their derivatives) can be transformed into oxybutyric acid or directly into aceton, and, finally, which of these substances occur in food, fatty or protein; in other words, which may be considered as sources of aceton bodies?

Borchardt and Lange decided to repeat the experiment of Embden and others with perfusion of the liver, by feeding the same substances to men. As these experiments of Embden et al. bear mostly on the forma-

13. Wien. klin. Wchnschr., 1906, p. 334.
14. Ztschr. f. exper. Path. u. Therap., 1906, iii, 466.
15. Hofmeister's Beitr., 1907, ix, 116.

tion of aceton from fat, I shall mention this part of their paper under that division of my subject dealing with this side of the question. The experiments of Borchardt and Lange will also receive the consideration which their excellent work deserves, but their conclusions may be briefly stated as follows: That those amido products of albumin digestion which lead to formation of aceton do so by being converted into their corresponding fatty acids and are oxidized to aceton in this way.

There is, of course, ample proof that aceton can be formed from protein tissue, but, as this formation always takes place over fatty acids, protein may, in the light of investigations previously quoted, be considered not as a source of aceton *sui generis*, but merely as a source of amido acids which, in their turn, by breaking off of the amido group are converted into fatty acids and then into aceton.

B. ***Origin of Aceton from Carbohydrates.***—The only reference I have found to this side of the question is a work by Neuberg and Blumenthal.[6] They quote Emil Fischer as believing that carbohydrates are derived from fat, and Magnus Levy, who believes that in the breaking up of hexoses, lactic acid is first formed according to the following equation: $C_6H_{12}O_6 = 2CH_3—CHOH—COOH$. This acid goes easily into formic acid and acetaldehyd, $CH_3—CHOH—COOH = H.COOH + CH_3.CHO$. With this as a working basis, Neuberg and Blumenthal develop a very pretty hypothesis. By condensation of two molecules of acetaldehyde an aldol is formed, $2CH_3.CHO = CH_3—CHOH—CH_2—COH$ (β-oxybutyraldehyde), and this, in turn, by shoving of oxygen in between molecules or by splitting off of water, forming crotonaldehyde—$CH_3.CHCH.COH$—and then adding it, butyric acid is formed. By repeated condensation of aldol and crotonaldehyde and subsequent reduction, the higher fatty acids may be supposed to be formed. They think that the question of formation of aceton from fat may be equally well regarded as a question of aceton formation from carbohydrates, also that the hypothesis is rather stretched in supposing that fatty acids must be broken up to butyric acid and this, in turn, be subjected to a succession of complicated reactions before aceton can be formed; so they prefer to believe that the same substances form aceton as form fat, namely, carbohydrates.

The above view has not been generally accepted; in fact, I know of no work published which deals with this novel theory of Neuberg and Blumenthal. *In vitro* and *in vivo* are two entirely different questions, and until laboratory experiments can be reproduced, in a measure, in the body, their importance in metabolism problems is somewhat vitiated. There is no proof that sugar or any carbohydrate increases aceton, and

thousands of instances where acetonuria has been held in abeyance by the ingestion of sugar. My personal belief is that the question of the derivation of aceton from carbohydrate has but little importance, if any.

C. *Origin of Aceton from Fat.*—Here it is that we meet with the probable solution of the whole question of the source of the aceton bodies. It has been known, or at least conjectured, for a great while that fat or some component of fat has the most to do with the formation of aceton, and, to my mind, the work of Embden, Salomon, Borchardt and others has put the subject on a very sound basis from which there does not seem to be any probability of its being dislodged.

Geelmuyden (quoted by Hagenbeck[16]) found that fat containing no low fatty acids (beef tallow) diminished and prevented aceton, whereas butyric acid increased it, and stated that the varying acetonuria on fat diet, for instance butter, depended on the amount of the volatile fatty acids present. Hagenbeck took up this particular point, using the calcium salt of butyric acid. His object was to study aceton, so he disregarded β-oxybutyric acid entirely. He confirmed Geelmuyden's observation, and thinks the presence of aceton is dependent on the lower fatty acids. He states, furthermore, that *in vitro* butter, plus potassium permanganate and sodium hydroxid, gives rise to aceton.

Schwarz[17] found that in health there was no increase of aceton after fat ingestion, but, in diabetes, fatty diet, especially butter, caused marked increase, and this increase was higher if aceton was high before the experiments.

Waldvogel and Hagenberg[18] studied the effect of over-nourishment with fat and fatty acids on healthy organism, selecting themselves for study, and found that, despite abundant food, with certain amounts of fat and fatty acids, the aceton excreted was normal. Just the opposite view is held by Schumann-Leclercq,[19] who states that fat must be regarded as the principal cause of aceton, no matter if there is disturbance of body or food fat, or whether the patient is fasting, on fatty diet, or on meat diet, and, furthermore, that carbohydrates inhibit aceton by protecting the labile fat from combustion to aceton.

Mohr and Loeb[20] found after 200 grams of butter that β-oxybutyric acid was increased, but there was no increase after 300 grams sesame oil, which they attribute to absence of volatile fatty acids. By increasing

16. Centralbl. f. Stoffwechsel-u. Verdauungskr., 1900, p. 33.
17. Id., p. 2.
18. Ztschr. f. klin. Med., 1901, xlii, 443.
19. Wien. klin. Wchnschr., 1901, p. 237.
20. Centralbl. f. Stoffwechsel-u. Verdauungskr., 1902, p. 193.

or diminishing fatty food they observed an increase or diminution in oxybutyric acid, whereas the aceton was unaffected. They also noticed that both aceton and oxybutyric acid were diminished after glycerin, and confirmed Rumpf's observation of increase of β-oxybutyric acid after sodium butyrate, only they used pure butyric acid neutralized with NaOH.

Neuberg and Blumenthal[6] refute the idea of aceton formation from fat and contend that if it takes place it is due to bacterial activity in the intestine. Johannes Müller was the champion of this view, but Lüthje, quoted by Neuberg and Blumenthal, discovered in a diabetic girl that calomel had no effect on aceton and diacetic acid. The strongest proof that Neuberg and Blumenthal offer is that it is only per os that butyric acid increases the output of aceton, the subcutaneous injections having no effect.

It is supposed that the following reactions take place in the bowels,

$CH_3\text{-}CH_2\text{-}CH_2\text{-}COOH$ $\qquad$ $CH_3\text{-}CHOH\text{-}CH_2COOH \longrightarrow$

Butyric acid. $\qquad$ β-oxybutyric acid.

$CH_3\text{-}CO\text{-}CH_2\text{-}COOH$ $\qquad$ $CH_3\text{-}CO\text{-}CH_3$

but Neuberg and Blumenthal state that the pure chemical oxidation of butyric acid with nitric acid takes place in the gamma position, and succinic acid, $COOH—CH_2—CH_2—COOH$, is formed, or, if oxidation with chromic acid, there is a shattering of the molecule with the formation of CO_2 and acetic acid. They prefer to believe in the carbohydrate origin of aceton, as previously stated.

Baer[7] has found that when much albumin is ingested the acidosis is diminished, much carbohydrate causes it to disappear, while much fat, especially the lower fatty acids, increases it. On a mixed diet, however, he states that fat ingestion causes no acidosis; the few exceptions that Waldvogel found are to him not proof against this view, but Baer believes that the degree of acidosis, that is the amount of aceton bodies excreted, is due not so much to the food ingested as to the disease itself, as the fatty acids or esters are in sufficient quantity in the body to account for all the aceton.

Schwarz,[21] in a study of diabetes, found a great difference in aceton output in (a) healthy people and non-diabetics and in (b) diabetics. In the former, he found only a very slight increase of aceton after fat, and this was seen only when the fat intake was very large, but if the carbohydrates are withdrawn and the healthy subject is starved, making of him an acetonuric, butter is found to increase the aceton. These subjects can not, however, be classed as healthy when subjected to such

21. Deutsch. Arch f. klin. Med., 1903, lxxvi, 233.

abnormal conditions. As aceton has been found in pregnancy (Stolz[22]), typhoid fever (Bernert[23]), phosphorus poisoning (Walko[24]), also after chloroform and other narcotics, in inanition, and carcinoma of the gastrointestinal tract, it seems to be an expression of abnormal fat destruction.

In diabetics Schwarz has found aceton increased with all sorts of fats, although pig's fat did not exert so marked an influence as did other fats. The higher fatty acids were found to increase the aceton, though this increase was not as noticeable as after the lower fatty acids.

An increase of aceton after ingestion of acids of the oleic acid group, $C_nH_{2n}—2O_2$, is rarely seen, and Schwarz supposes, as these acids are much more sensitive to oxidative processes outside the body than are the fatty acids, that they are more easily burned up in the body. Aceton can be formed from body fats over the butyric acid route, either by successive splitting off of CO_2 or by breaking up of long C chain, and the four carbon chain is oxidized in the β position, which is a peculiarity of the organism, as by chemical means this can not be brought about. Schwarz made a few experiments with β-oxybutyric acid in health and in diabetes, and found that a dog could use three grams pro Kg. body weight without a trace appearing in the urine. In mild diabetes, an amount which a healthy person could use up without an effort produced an increase of aceton only, whereas in severe diabetics not only aceton was seen, but also unchanged β-oxybutyric acid. Aceton was not completely used up by normal man.

As a result of his studies Schwarz makes the following conclusions:

1. In health fat causes only slight increase of aceton.

2. It is probable that in many conditions, such as starvation, phosphorus poisoning, narcosis and coma, aceton is due to melting of body fat, although not all wasting diseases are accompanied by aceton.

3. In severe diabetes, aceton may be derived from the fat of food or from body fat if the carbohydrate intake is cut down. The intestinal canal does not seem to play an important rôle in aceton formation.

4. The total aceton output is subject to variation even with constant diet, and the amount of β-oxybutyric acid excreted is very large; it can be as high as 70 per cent. or even more.

5. The higher fatty acids do not increase the aceton bodies as do the lower acids; the acids of the oleic acid group least of all.

22. Arch. f. Gynäk., 1902, lxv, 531.
23. Ztschr. f. Heilk., 1902, xxiii, 113.
24. Quoted by Stolz (loc. cit.).

6. Butter increases the aceton more than do the animal fats. The action of oils is dependent on the presence of fatty acids.

7. In normal people, but especially in severe diabetics, ingested β-oxybutyric acid is insufficiently combusted if no carbohydrates are taken, whereas aceton is badly used up in any case, and can not be regarded as an intermediary metabolic product, although β-oxybutyric acid may be.

8. Lipemia is higher in severe diabetes than in mild cases, is seen even with absence of fat from the diet, apart from coma, and can be associated with no symptoms for a long time, but is always associated with excretion of aceton bodies.

9. Alimentary lipemia is seen in severe cases of diabetes after large amounts of fat.

Geelmuyden[25] thinks that the aceton bodies are formed in large amounts in health, but are changed again to other substances. In health, diacetic acid and oxybutyric acid are well burned up by organisms, but aceton is not; hence it should not be regarded as a product of intermediary metabolism, as are the other two acids. These he regards as normal intermediary products, but, being burned up as soon as formed, are not excreted. The fact that carbohydrate inanition is the sole cause of acetonuria is explained by Geelmuyden on the belief that carbohydrates unite with aceton in intermediary metabolism by synthesis as glycuronic acid, which process is necessary for the further change of the aceton bodies; failure of this synthesis or limitation of the same causes a collection of aceton bodies and their subsequent excretion. He regards fat as the principal mother substance of aceton.

Knoop,[26] realizing the difficulty of studying the intermediary cleavage products of fatty acids, states that the only way to study this properly, is by combining these acids with a substance which is attacked with difficulty by the organism, as otherwise the fatty acids are broken down so completely and so quickly that no intermediary products can be found. He recalls the fact that tyrosin, phenylalanin and a aminocinnamic acid are completely oxidized in the body; phenylproprionic acid and cinnamic acid are oxidized to benzoic acid, whereas phenylacetic acid and its derivatives, mandelic acid and phenylamido acetic acid, are unchanged, with the exception of the last, which simply has its NH_2 group replaced by the hydroxyl radical OH. It will be recalled by consulting Table I that all these substances have the benzene (C_6H_5) group in common; so why should the other bodies be oxidized and not the phenyl-

25. Ztschr. f. physiol. Chem., 1904, iv, 128.

26. Hofmeister's Beitr., 1904-5, vi, 150.

TABLE 1.

Ingested.	Acid.	Excreted.		Change Observed.
Benzoic acid	$C_6H_5.COOH$	Benzoic acid	$C_6H_5.COOH$	Unchanged.
Phenylacetic acid	$C_6H_5CH_2.COOH$	Phenylacetic acid	$C_6H_5.CH_2.COOH$	Unchanged.
Mandelic acid	$C_6H_5CHOH.COOH$	Mandelic acid	$C_6H_5.CHOH.COOH$	Unchanged.
Phenylamidoacetic acid	$C_6H_5 CH(NH_2).COOH$	Mandelic acid	$C_6H_5.CHOH.COOH$	Detritrified.
Phenylproprionic acid	$C_6H_5.CH_2CH_2 COOH$	Benzoic acid	$C_6H_5.COOH$	Oxidized at β-carbon atom.
Phenyl β-lactic acid	$C_6H_5.CHOH.CH_2 COOH$	Benzoic acid	$C_6H_5.COOH$	
Phenyl β-ketoproprionic acid	$C_6H_5.CO.CH_2.COOH$	Benzoic acid	$C_6H_5.COOH$	
Cinnamic acid	$C_6H_5.CH:CH.COOH$	Benzoic acid	$C_6H_5.COOH$	
Phenylalanin	$C_6H_5.CH_2 CH(NH_2).COOH$	Disappears		Completely oxidized.
Phenyl α-lactic acid	$C_6H_5.CH_2.CHOH.COOH$	Disappears		
Phenyl α-ketoproprionic acid	$C_6H_5.CH_2.CO.COOH$	Disappears		
α-Amido cinnamic acid	$C_6H_5.CH:C(NH_2)COOH$	Disappears		
Phenylbutyric acid	$C_6H_5.CH_2.CH_2.CH_2.COOH$	Phenylacetic acid	$C_6H_5.CH_2.COOH$	Oxidized at β-carbon atom.
Benzoyl proprionic acid	$C_6H_5.CO.CH_2CH_2COOH$	Phenylacetic acid	$C_6H_5.CH_2.COOH$	
Phenyl iso crotonic acid	$C_6H_5.CH:CH.CH_2.COOH$	Phenylacetic acid	$C_6H_5.CH_2.COOH$	Oxidized at δ-carbon atom.
Phenylvaleric acid	$C_6H_5.CH_2CH_2CH_2CH_2.COOH$	Benzoic acid	$C_6H_5.COOH$	

acetic acid or its derivatives? It is not possible that phenylproprionic acid is oxidized to phenylacetic acid, or else this substance would appear in the urine, or at least one of its derivatives, so Knoop believes that the oxidation process takes place not in the *a* position, but at the *β* carbon atom. Whether the oxidation of the side chain is the rule or not, Knoop proposes to decide by studying the higher homologs of phenylproprionic acid or of its derivatives.

Without going into detail with Knoop's experiments with individual acids, it will suffice to reproduce his table with a short summary of his conclusions as given by Folin.[1]

"When ordinary fatty acid derivatives are linked to the benzene group, C_6H_5, and the resulting compounds are fed to dogs, the fatty acid chains are broken down by oxidation of the carbon atom third from the end of the chain and the intervening two carbon atoms are split off. In other words, not one, but two carbon atoms are split off at a time, and only so many are split off as can be taken two at a time and still leave, at least, one carbon atom attached to the benzene ring.

"If the fatty acid side chain attached to the benzene radical contains only one or only two carbon atoms, these can not be split off, and such compounds will pass through the organism unchanged or but little altered. With three or with four carbon atoms in the chain two can be split off, while with five or six carbon atoms in the chain four can be removed."

Satta[8] thinks that there is no doubt that fatty acids are the source of aceton, but questions if the splitting of fatty acids takes place normally over *β*-oxybutyric acid or aceton. In favor of the view that normally this does not occur, he writes as follows:

1. The constant excretion of small quantities of aceton by the kidneys and lungs leads one to believe that aceton is a normal product of metabolism, although this does not mean that the aceton thus formed is formed in the same way as the aceton seen under pathologic conditions. The small amount of aceton and absence of *β*-oxybutyric acid in normal urine makes one think that either the quantity of the precursors of aceton is small, or else the aceton is not derived from the same source as pathologic aceton; that is, is not formed from oxybutyric acid. The latter is never seen normally, even when the excretion of aceton exceeds the usual amount, despite carbohydrate ingestion, and L. Schwarz found no oxybutyric acid in normal persons, even when aceton was as high as 0.61 grams a day. Satta says that *β*-oxybutyric acid is not a normal metabolic product and that the normal aceton comes from another mother substance and not from *β*-oxybutyric acid.

2. It is impossible to cause the disappearance of aceton. Even with much carbohydrate ingestion the normal aceton can not be made to disappear, while under the same conditions the aceton output is markedly diminished.

3. The normal organisms can burn up quite readily β-oxybutyric acid and diacetic acid, although there have not been many experiments with the latter, while, on the other hand, the oxidation of aceton is not only deficient in diabetics, but also in normal individuals.

While to Satta's mind the fact that abnormal aceton is a product of fat splitting, yet this does not help in explaining the presence of normal aceton. If a person is fed on excessive protein and carbohydrate food the normal aceton still appears. In this case no fat has been ingested and no fat is being broken down. On the other hand, by withdrawing carbohydrates from the food, forcing the organism to draw on its own heat-supply, aceton is increased, and all that is necessary in order to diminish it again is the ingestion of carbohydrates.

In this connection it may be well to consider how these antiketoplastic bodies act. One view is that these stuffs act directly or indirectly, increasing the oxidation of β-oxybutyric acid to aceton, but this is scarcely possible, as β-oxybutyric acid, when ingested, is burned up with no increase of aceton, and, as aceton is poorly attacked, the oxidation of β-oxybutyric acid over diacetic acid and aceton can not take place. Another view advanced by Geelmuyden[25] is that a synthesis takes place between β-oxybutyric acid and carbohydrates, probably glycuronic acid, by means of which the aceton formation is hindered, and failure of this synthesis on carbohydrate diet is expressed by acetonuria. Satta believes that this synthesis does not take place between β-oxybutyric acid and carbohydrates alone, but also between the precursors of β-oxybutyric acid and carbohydrates. That the pairing of the former is not with glycuronic acid alone is shown by the fact that levulose and pentose act antiketoplastically, but do not form glycuronic acid. Still a third view is that, in the presence of these antiketoplastic bodies, no β-oxybutyric acid is formed from fat, consequently no diacetic acid and aceton.

Against the intestinal origin of aceton formation Satta makes the following objections:

1. Purges do not diminish aceton, but often have the opposite effect, and even salol and benzol, two well-known intestinal antiseptics, are frequently followed by increase of aceton.

2. The gastrointestinal tract does not contain considerably more aceton than do other organs, and Magnus Levy found less aceton in the gastrointestinal tract of a diabetic than in the other organs.

3. If aceton is formed in the gastrointestinal tract, there should be a direct relation between proteid decomposition and aceton, but Satta found that sulphur diminished when aceton was increased and went up if aceton remained constant or sank.

4. The aceton of inanition could not be explained on this basis, for, if nothing is taken into the stomach, how can aceton be formed from protein decomposition in the intestines? Müller, however, states that albumin is still decomposed, but against this it may be stated that:

(a) Inanition acetonuria increases while the amount of gastrointestinal contents diminishes.

(b) If the stomach and intestines are analyzed, it is found that only 16.23 grams of β-oxybutyric acid can be obtained.

(c) If it is believed, as Müller himself holds, that aceton is derived from fat, then this militates against the gastrointestinal theory, as fat is scarcely ever present.

(d) The immense amounts of aceton seen in coma, and when patient has fasted three and four days, lead one to think that the building place of aceton is within the cells, although in which organ is still undecided. Satta suggests that in those organs having the most to do with the utilization of fat, namely, the glandular organs, there should be found more oxybutyric acid and its descendants (Knoop's experiments show that a fatty acid molecule through successive oxidation in the β position, finally yields one molecule β-oxybutyric acid).

Baer[27] studied the effect of glycuronic acid on acidosis, working on the idea of Geelmuyden,[25] that glycuronic acid is the underlying feature of acidosis. He gave dogs camphor in order to cause increase of paired glycuronic acid, and hence withdrawal of this acid from metabolism, but he found no increase of aceton or of β-oxybutyric acid. In fact, he produced a diminution of β-oxybutyric acid and aceton, but in order that the objections should not be raised, that, as camphor is an excitant, it might cause increased combustion of aceton bodies, he substituted chloral hydrate. In this case he found the acidosis to be diminished and that oxybutyric acid almost disappeared. As the dog was somnolent, he again made a substitution with morphin, and, finding that there was an increase of acidosis, he gave chloral hydrate again, with an immediate diminution of aceton.

If by withdrawal of glycuronic acid the acidosis is diminished, or if in excretion of glycuronic acid, with glycosuria, no acidosis appears, it would seem that glycuronic acid is itself the source of aceton bodies. Indeed, a similar idea was advanced by Flückiger as follows:

27. Ztschr. f. klin. Med., 1905, lvi, 198.

$COH(CHOH)_4.COOH$ (glycuronic acid) = $C_4H_8O_3$ (oxybutyric acid) + CH_2O_2 (formic acid) and CO_2, but this theory does not assist us much in the solution of the question, as we know that aceton may be derived from many sources.

Baer is inclined to believe that in fasting glycuronic acid is not derived from pre-existing carbohydrates, but from protein, as suggested originally by Loewi or from other groups having nothing to do with carbohydrate production, perhaps from mother substance of aceton bodies. It is not improbable that decomposition products arise together with glycuronic acid and by further combustion cause diminution of acidosis.

Borchardt,[28] in discussing the sources of aceton bodies, says that fat is ketoplastic and glycerin antiketoplastic. As fat is resorbed from intestines and appears in chyme as neutral fat by synthesis with glycerin derived from the body, he suggests that the ketoplastic action of fat is due not so much to the acid formers as to withdrawal of the antiketoplastic substance, glycerin.

This view is further supported by the fact that fatty acids injected subcutaneously are not ketoplastic. Geelmuyden found no acetonuria after two grams of butyric acid were given in that way. Waldvogel found no aceton bodies after the administration of olive oil, and it is now settled that fat without fatty acids diminishes aceton body excretion.

The difference in action of ingested fatty acids and injected fatty acids is very easily explained by Borchardt as follows: If given per os, there is a synthesis with the glycerin of the body, with the formation of neutral fat-tri glycerids of the ingested fatty acids. This glycerin, being derived from the body, has no power to form sugar (which ordinarily it accomplishes very easily), and it loses its antiketoplastic property on this account.

It will be remembered that carbohydrates lessen the output of the aceton bodies. If the fat is injected subcutaneously, there is no synthesis with glycerin, no withdrawal of glycerin from the body, the glycerin retains its sugar-forming antiketoplastic property, and there is no increase of aceton. It is this withdrawal of glycerin from the body and not the action of the fatty acids themselves that accounts for the ketoplastic action ascribed to the latter. Although apparently in favor of this ingenious view, Borchardt remains non-committal, preferring that time and future experiments should furnish the proof. This work, to my mind, refutes the arguments of Neuberg and Blumenthal.[6]

Embden and Kalberlah[29] refer to a previous series of experiments in

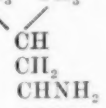
28. Centralbl. f. d. ges. Physiol. u. Path. d. Stoffwechs-u, 1906, viii, 121.
29. Hofmeister's Beitr., 1906, viii, 121.

which they showed that the liver was the chief building station of aceton. Embden, Salomon and Schmidt[30] go still further and study from what substance aceton is formed. As their work is of great interest, I have chosen to review it at length. The above authors start their work with two postulates:

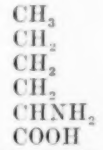
1. If aceton is a breaking down product of a substance, it ought to display the same characteristic structure as the mother substance from which it is derived.

2. Appearance of aceton after perfusion leads to the idea that addition of substances to the blood ought to increase aceton, as it is bound up with difficulty in the liver.

They added glycocoll, alanin, glutaric acid and asparagin to perfused blood, but found no increase in aceton. After leucin,



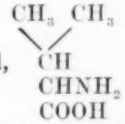
however, there was a marked increase and they suggest that aceton may be derived from the iso propyl group. If that is so, then an isomeric compound of leucin should



not give it, and they used *a* amido normal caproic acid,

and found, as they supposed, that the aceton remained within the limits of that found after perfusion of liver with blood, so that the increase of aceton is probably not due to the iso propyl group.

They tried the next lower *a* amido iso valeric acid,



which did not cause increase of aceton, for there was neither a splitting of carbon from carboxyl group, nor a splitting between the *a* and β carbon atom.

v. Noorden and Embden suggested that there is a splitting between the β and γ carbon atom, which would explain the aceton seen after leucin, and not after amido valeric acid, as such splitting would not produce aceton here.

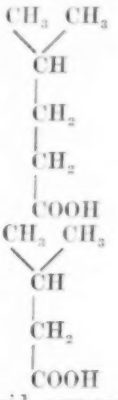
Phenyl proprionic acid, $C_6H_5.CH_2CH_2COOH$, and cinnamic acid, $C_6H_5.CH:CH.COOH$, are changed in the organism to benzoic acid,

30. Id., p. 129.

$C_6H_5:COOH$, and hippuric acid, $C_6H_5CO:NH.CH_2COOH$, and it will be remembered that Knoop found that γ phenyl butyric acid was split up to phenyl acetic acid, $C_6H_5CH_2COOH$, and appears as such, whereas phenyl valeric acid, $C_6H_5(CH_2)_4.COOH$, goes into hippuric acid. Also it was found that β-phenyl lactic acid, $C_6H_5.CH_2.CHOH.COOH$, and benzoyl acetic acid, $C_6H_5CO.CH_2COOH$, appear as hippuric acid; benzoylproprionic acid, $C_6H_5.CO_2CH_2CH_2COOH$, and phenyl iso crotonic acid, and $C_6H_5CH:CH.CH_2.COOH$, as phenylacetic acid, and in all these there is a splitting between the α and β carbon atoms.

Embden, Salomon and Schmidt now suggested that the NH_2 group might be the cause, so they took the corresponding fatty acids,

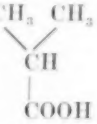
iso butylacetic acid,



and iso valeric acid,

and found that the iso butylacetic acid, corresponding to leucin, formed no aceton, whereas the iso valeric acid, corresponding to amid valeric acid, was a strong aceton builder, just an opposite effect from leucin and amido valeric acid. The last follows the same law as the splitting up of the chain, as Knoop found, namely, there was a cleaverage between the α and the β carbon atom.

If this view is applied to iso butylacetic acid, which in structure is like iso valeric acid, namely, that there is a splitting between the α and β carbon atoms, then iso butyric acid,



should be formed, and, if this is so, then this acid should give no aceton, which they found to be the case. The three homologs, iso butyric acid, iso valeric acid, and iso butylacetic acid, as regards their aceton building properties, behave exactly as do the aromatic fatty acids in their side

chains, and Knoop's experiments hold good for the aliphatic fatty acids. Why leucin and amido iso valeric acid are split up differently from their corresponding fatty acids is explained by Embden and his co-workers:

Leucin and amido iso valeric acid are changed by a splitting up of the carboxyl group into substances with one less carbon atom.

Whether the leucin is changed to iso valeric acid by oxidation of its carbon atom after denitrification, or whether amido iso valeric acid is converted into iso butyric acid in the same way, or if only the precursors of these fatty acids are formed—for instance,

iso amylic alcohol, CH_3 CH_3
\ /
CH
|
CH_2
|
CH_2OH

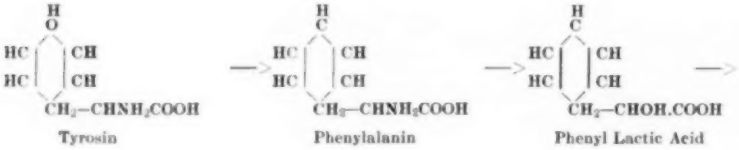
or iso valeraldehyd, CH_3 CH_3
\ /
CH
|
CH_2
|
C_2OH

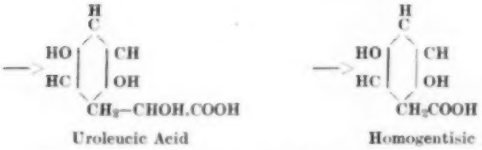
from leucin—they do not say. Whichever way they are split up, their further cleavage after splitting of carboxyl group follows the same law as that of fatty acids. Leucin, according to this, would be split up just the same as iso valeric acid and the amido iso butyric acid like iso butyric acid. Therefore, leucin perfusion gives rise to aceton as does perfusion with iso valeric acid, and amido iso valeric acid does not, as is the case with iso butyric acid.

Magnus Levy showed that oxybutyric acid can form aceton in the animal organism, and Embden et al. found this to be the case in perfusion of liver, where almost ten times as much aceton was formed as is seen with perfusion of normal blood. Perfusion of muscle led to negative results. Since oxybutyric acid is probably formed by oxidation from butyric acid, they tried the latter and found that aceton was formed, doubtless with the intermediary formation of oxybutyric acid.

They studied perfusion with l-tyrosin, $HO\text{-}C_6H_4\text{-}CH_2\text{-}CHNH_2\text{-}COOH$, and racemic phenylalanin, $C_6H_5\text{-}CH_2\text{-}CHNH_2\text{-}COOH$, which it will be seen, are amido acids united to the benzene radical, and found that both produced aceton. The phenylalanin minus the amido group or β phenyl *a* lactic acid, $C_6H_5\text{-}CH_2\text{-}CHOH\text{-}COOH$, also produced aceton, though not to such a marked degree as tyrosin and phenylalanin. As in

these substances the aromatic nucleus is burned up in the body, the next point to prove was whether aromatic substances themselves could produce aceton, in other words, if the aceton formation is in any way connected with the combustion of the aromatic nucleus. They selected β phenyl β lactic acid, C_6H_5-CHOH-CH_2-COOH, phenylacetic acid, C_6H_5-CH_2-COOH, and cinnamic acid, C_6H_5-CH:CH-COOH, and found that all of these failed utterly to produce aceton, and they conclude that the source of aceton in tyrosin, phenylalanin, and phenyl *a* lactic acid is the easily attacked aromatic nucleus, while in β phenyl β lactic acid, phenylacetic acid, and cinnamic acid, as the nucleus is not oxidized, there is consequently no aceton. How the benzene ring is utilized to form aceton is not certain, but, according to Neubauer and Falta, phenylalanin is changed to uroleucic acid, then to homogentisic acid, and in this acid the benzene ring is attacked, and Embden et al. confirmed this by finding aceton increased by perfusion with the latter.





Embden, Salomon, and Schmidt make several conclusions, which, briefly put, are that the aliphatic monamido monobasic acids are broken down to a body containing one less carbon atom, probably the corresponding fatty acid, and as such they are burned up as fatty acids are, namely, by oxidation in the β position.

Without detailing the important contributions of Baer and Blum,[31] it may briefly be stated that after a very careful study of the result of giving fatty acids to diabetics, they conclude that branched fatty acids, with an even group of carbon atoms, are productive of β oxybutyric acid and with this, aceton, whereas fatty acids, with 3 or 5 carbon atoms in a straight chain are not; and especially productive of oxybutyric acid are those acids where oxidation takes place in the β position. Of course, when β oxybutyric acid was increased, aceton was increased also, lending

31. Arch. f. exper. Path. u. Pharmakol., 1906-7, lv, 89, and lvi, 92.

additional weight, if more were necessary, to the belief that aceton is an end-product of β-oxybutyric oxidation.

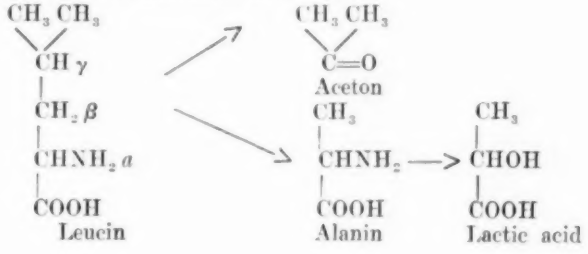
In order to see if Embden, Salomon and Schmidt's observations on the perfused liver could be repeated by feeding the same substances, Borchardt and Lange[14] experimented on themselves. They put themselves on a carbohydrate free diet and produced constant aceton output, then they gave themselves amido acids, beginning with glycocoll, CH_2NH_2-COOH, and found no increase, but rather a diminution of aceton. Embden[28] had found the same thing with perfusion. With alanin, CH_3-$CHNH_2COOH$, there was a diminution of aceton, confirming previous observations of Embden et al. The cause of this is due to the conversion of alanin into lactic acid by denitrification,

$$\begin{array}{lll} CH_3 & CH_3 & \\ | & & \\ CHNH_2 & CHOH & \text{Lactic acid} \\ | & & \\ COOH & COOH & \end{array}$$

and this acid has been found by Neuberg and Langstein after feeding rabbits on alanin and also by Embden in his perfusion experiments. Studies by Satta have shown that lactic acid is an antiketoplastic body, so that the explanation seems to be a suitable one.

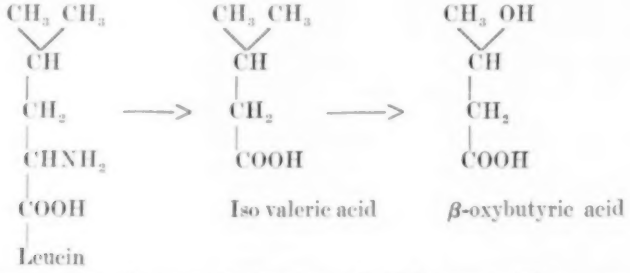
The next acid to be experimented with by Borchardt and Lange was the amid of the dibasic aspartic acid, asparagin, $COOH.CHNH_2.CH_2$-$CONH_2$. They found this produced a decided diminishing effect on the excretion of aceton bodies, as did Embden, Salomon and Schmidt. Glutaminic acid, *a* amido glutaric acid, $COOH$-CH_2-CH_2CHNH_2-$COOH$, was found in perfusion to have no influence on aceton bodies and on feeding they found the same thing.

Leucin caused a marked increase in aceton, as Embden found. Embden, Salomon and Schmidt believe this occurs by splitting of molecule between β and γ carbon atoms, giving rise to aceton directly. In this case lactic acid should be formed from lower half, but Embden could not find this, nor could Borchardt and Lange.



It seems to me that were the leucin split up in this way the aceton should be decreased, as lactic acid is an antiketoplastic substance (Satta).

Baer and Blum give another explanation, according to the law that fatty acid derivatives with substitution at the *a* carbon atom behave exactly as does the next lower fatty acid; in this way iso valeric acid would be formed, which, in turn, by substituting an hydroxyl group for a methyl group would be converted into β-oxybutyric acid, as shown by the following formula:

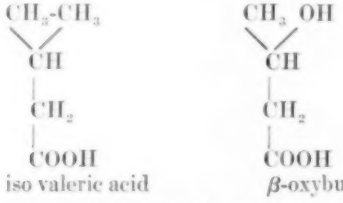


This seems to be the way of cleavage, for if it were split up over alanin and lactic acid sugar should be formed, as the last two substances are known to be conspicuous sugar formers, while leucin is known to have no effect on sugar output.

Borchardt and Lange conclude their interesting paper with the following conclusions regarding the cleavage of fatty, oxy and amido fatty acids:

1. In the formation of aceton bodies, oxybutyric acid is first formed, from which by further oxidation diacetic acid is formed, and, finally, by cleavage of carboxyl group aceton is produced (Minkowski).

2. Amido and methyl groups united to a carbon atom can be substituted by a hydroxyl radical; in branched fatty acids, with two terminal methyl groups, one of the methyl groups is substituted by a hydroxyl, for instance,



3. *a*-oxy and *a*-amido acids behave as do the next lower fatty acids (*a* amido valeric acid like butyric acid, leucin like iso valeric acid).

4. Unbranched fatty acids with an even number of carbon atoms and with the group CH_2-CH_2-CH_2-COOH can be oxidized in the β position, split in the same position and again oxidized in β position, until they are broken down to β-oxybutyric acid.

Branched fatty acids with uneven carbon atoms are probably split in same way and lead to oxybutyric acid formation.

MODERN THEORIES AS TO CAUSE OF ACIDOSIS AND COMA.

Lépine[32] says that acidosis does not explain all the symptoms of coma, especially the pulse and dyspnea, and quotes Klemperer and von Noorden as holding the view that coma is due to an unknown toxin in the blood. Sternberg (quoted by Lépine) has shown that after ingestion of β amido butyric acid there is acceleration of the pulse and respiration and appearances of coma, and that one gram per kilogram of body weight is fatal. β-oxybutyric acid, to the extent of nine grams, on the other hand, has been injected into a dog weighing 7 kg. without any ill effects, and he suggests that β amido butyric acid may produce β-oxybutyric acid with splitting off of NH_3.

CH_3CHNH_2-CH_2-COOH + H_2O = CH_3.CHOH.CH_2.COOH + NH_3.

One explanation for the increase of NH_3 seen in diabetic coma is thus offered, and the second source would be the protein tissue, as will soon be shown.

Lépine thinks the amido butyric acid is derived from the nitril of amido butyric acid as follows:

CH_3-$CHNH_2$.CH_2.CN + $2H_2O$ = CH_3-$CHNH_2$-CH_2-COOH + NH_3.

Gautier (quoted by Lépine) has found that albuminous substances contain complex nitrils. Some are innocuous, but by the action of certain reagents nitrils can become very poisonous, as cinnamic nitril, which produces symptoms analogous to hydrocyanic acid poisoning. Lépine's theory based on Gautier's observations and his own work is, that not the β amido butyric acid or β-oxybutyric acid, but rather the complex nitrils of protein tissue are the cause of acidosis. In support of this view he concurs with Fiquet in recommending phenol in diabetes, as combinations of this with nitrils renders them innocuous, and believes it should be tried. This very suggestive work of Lépine does not seem to have been followed up, and, despite the fact that only *a* amido acids are seen after protein cleavage, there are a great many things in favor of his theory, which require further study to be put on a firm basis.

32. Semaine méd., 1900, p. 399.

33. Deutsch. med. Wchnschr., 1900, p. 757.

Spitzer[33] does not lay much stress on the β-oxybutyric acid theory of acidosis, as even diabetics can use up a good deal of oxybutyric acid, and in pancreatic diabetes no acidosis can be produced with oxybutyric acid. He agrees with Magnus Levy that the poverty of the organism in fixed alkalies is not the cause, as Naunyn held. Spitzer holds to the view that carbohydrates are to be regarded as the underlying condition, as cases of diabetes are constantly met with where acidosis appears on going over to a carbohydrate free diet. Here no increase of acid is ingested, the main reason for the appearance of coma being that in breaking down of carbohydrates, substances are formed which, uniting with the decomposition products of protein and fat, render easy the oxidation to CO_2 and H_2O. Absence of these substances, as is seen in carbohydrate hunger and in diabetes, leads to acidosis, as the oxidative power of the organism is not enough in itself.

The disturbance of the carbohydrate metabolism, preventing oxidation of protein and fatty decomposition products, Spitzer believes to be due to psychic or physical trauma, for such cases are often seen leading to rapid death from acidosis. Again, cases of mild diabetes have been operated on, with rapidly ensuing coma after narcosis, and Spitzer does not agree with Naunyn that the narcosis has caused rapid tissue breakdown, explaining the acidosis, but thinks the time is too short for such an extensive destruction to take place, and that psychic shock best explains it. Spitzer reports a case of mild diabetes with absence of acidosis even after fasting, but which succumbed to coma after fracture of the clavicle. In this instance there was no oxybutyric acid, in fact, numerous cases have been published of coma with high NH_3 output, yet with no aceton or diacetic acid (Rumpf, Münzer, Strauss, quoted by Spitzer). Spitzer suggests that, as after the celebrated Piqûre, the liver is "frightened," shakes out all its glycogen and loses the power to hold back sugar coming to it.

Grube[34] has concisely summarized the four main theories of diabetic coma, and I shall briefly reproduce his remarks:

1. *Theory of Coma on Basis of Aceton Poisoning.*—He does not believe in this for three reasons: (a) aceton can be excreted for years with no symptoms of coma, (b) in a few cases of coma aceton has been absent, (c) after ingestion of aceton there is no intoxication, and even with large doses the symptoms are not those of diabetic coma.

2. *Uremic Theory.*—There is a wide difference between the two disorders, as uremia is never seen with healthy kidneys and coma very often is.

34. Arch. f. exper. Path. u. Pharmakol., 1900, xliv, 349.

3. *β-oxybutyric Acid Theory* (Stadelmann, Naunyn, Magnus Levy).—Stadelmann suggested that the symptoms of coma were due to increased acid formation, and believed that crotonic acid was the cause, but this was soon controverted by Minkowski and Külz, who found not crotonic acid, but β-oxybutyric acid. This theory, that of a β-oxybutyric acid intoxication, seems to be somewhat weakened by the studies of Walther, who produced symptoms similar to coma with hydrochloric acid and phosphoric acid. Furthermore, other acids, diacetic acid, lactic acid, and fatty acids are seen, and have each been held responsible for coma, though Magnus Levy claims they play no quantitative rôle.

4. *Unknown Toxin Theory* (Klemperer).—This theory holds that both coma and β-oxybutyric acid are caused by these toxins.

Grube seems to incline to this view (see Lépine), and experimented on cats with β amido butyric acid, producing coma in all of his twenty experiments, and, according to the amount of acid ingested, the severity of the coma was influenced, together with appearance of aceton and sugar. He has thus confirmed Sternberg's work, and in this he must be classed with Lépine, but he doubts whether β amido butyric acid is formed in the diabetic organism.

Magnus Levy[35] repeats in this work his former assertion that diabetic coma is an acid intoxication. The acidosis is so extreme in coma that the acid withdraws from the blood and tissue the alkalies of the carbonates and phosphates and destroys the vital groups of protein molecule, especially the proteid of the ganglia body cells. As a proof of this loss of oxidation power of organism, one sees in diabetic coma diminution of alkalies of blood and appearance of large quantities of β-oxybutyric acid in the blood.

Busse[36] agrees with the above, and states that in autopsies made on diabetics he has found parenchymatous degeneration of kidney and heart, and sometimes of liver, which he attributes to the action of β-oxybutyric acid.

Orlowski[37] studied the alkalinity of blood in diabetes and found it to be invariably lowered, due, as he says, to β-oxybutyric acid, which he regards as the underlying cause of coma, aceton, and diacetic acid being merely secondary. He gives a rather broad definition of acid intoxication, inasmuch as he regards the diagnosis as certain only when β-oxybutyric acid is found in the blood and urine, and when there is improvement in the condition with the use of alkalies. I should take exception

35. Id., 1901, xlv, 389.
36. München. med. Wchnschr., 1901, p. 1404.
37. Centralbl. f. Stoffwechsel., 1902, p. 31.

to the last statement, and I believe many clinicians would agree with me that many cases of coma do not recover under the use of sodium bicarbonate or alkalies in general, but they are nevertheless cases of coma. I recall a case, studied with Dr. Musser, where coma was prognosed several days before its onset, alkaline therapy was instituted intravenously, subcutaneously, per os, and by enteroclysis, despite which the patient gradually grew worse and died with the typical symptoms of diabetic coma. To make a diagnosis of such a severe condition on a therapeutic test seems to me to be unwise.

That aceton can cause autointoxication is shown in the report of two cases by Pettera,[38] but he specifically states that there was no resemblance between diabetic acidosis and his cases, nor was there ever found any sugar or β-oxybutyric acid. The condition is hardly to be confused with diabetic coma, although his report contradicts statements made by other observers that aceton is not toxic (Grube[24]). To these cases may be arrayed a third, reported by Palma,[39] of three attacks of autointoxication, when the only underlying condition was great increase of aceton in urine and probably in the breath, although Folin, in his Harvey lecture of 1908, said that the peculiar aceton odor of breath is not caused by aceton in the great majority of the cases.

Eppinger, in 1906, published two important papers dealing with acidosis which I consider worthy of detailed review. In the first contribution,[40] he reviews some of the previous work on this subject, starting with Salkowski's work on the utilization of tannin by herbivora. Tannin, it will be remembered, is amido ethyl sulphonic acid, $C_2H_7NSO_3$, or $CH_2NH_2CH_2SO_2OH$, and Salkowski found that herbivora used up tannin with the liberation of H_2SO_4, and that if the feeding of tannin were continued for any length of time the animals invariably died. This he believed due to the withdrawal of alkalies from the body by the acid, and found the bases of the urine increased after tannin. The same thing was noted after ingestion of H_2SO_4. Gäthgen, in attempting to corroborate this, fed tannin to dogs without any success, and ascribes the difference between his work and Salkowski's to the difference in chemical constitution of herbivora and carnivora.

Walther, according to Eppinger, laid the foundation of our modern view of acidosis, and found that if an acid which is not oxidized were introduced into rabbits, the CO_2 of the blood diminishes very rapidly, and when the height of the poisoning is reached it disappears entirely.

38. Prag. med. Wchnschr., 1905, p. 199.
39. Wien. klin. Wchnschr., 1906, No. 5.
40. Wien. klin. Wchnschr., 1906, No. 5.

He believes this is due to the combination of blood alkalies with the acid and, the blood being no longer able to extract the poisonous CO_2 from the tissues, there is an accumulation, and the animal succumbs to what he graphically terms "internal suffocation." He substantiates this view by noticing the remarkable beneficial effect of intravenous injection of alkalies in these cases. In dogs, on the contrary, he did not find this diminution of carbonic acid in the blood, and, as the fixed alkalies remain unchanged, he thinks the organism of a carnivorous animal has other means of protection against acid intoxication. This protection he ascribes to NH_3, which he found increased in the urine, and which he believes prevents the export of fixed alkalies from the blood.

Eppinger believes that the constitutional difference between carnivora and herbivora, suggested by Gäthgen, is not the fundamental reason for such divergence of results, but thinks the discrepancy is rather one of degree. Winterberg and Limbeck have shown that by gradually increasing the dose of the acid they could increase the usual lethal dose for a rabbit, which was accompanied by a slight increase of ammonia, and Spiro later showed that dogs could be killed by acid intoxication. These experiments tend to render the view of a "constitutional difference" in the two species untenable, but the question naturally arises, If in carnivora the ammonia is the main protection against acidosis, where is it stored up, for we know protein tissue is the only source? As rabbits have practically no ammonia for protection, Eppinger thinks that if nitrogenous bodies derived from protein decomposition are fed to rabbits they should save the animals from a fatal acid poisoning, and, furthermore, that their resistance should be accompanied with an increased output of ammonia in the urine.

Working on this hypothesis, he gave rabbits the fatal dose of hydrochloric acid, and followed immediately with amido acids, finding that glycocoll ($CH_2NH_2.COOH$), alanin (CH_3-$CHNH_2$-$COOH$) and aspartic acid ($COOH.CHNH_2.CH_2COOH$) all prevented acidosis. Two reasons are suggested: Either that this action was due to combination of the amido acid forming glycocoll hydrochlorate, which is excreted as such, or that oxidation takes place, setting ammonia free, which uniting with the acid renders it innocuous.

That the first was not the case was proved by the fact that the rabbit rapidly succumbed to an aliquot amount of glycocoll hydrochlorate. If the second procedure takes place, there should be more NH_3 found in the urine, which he showed to be the case. That the amount of ammonia derived from the amido acids is not enough to neutralize the acid, and that fixed alkalies are a factor, he proved by finding an increase of potas-

sium and sodium in the urine. Further confirmation of this is offered, as he found there was a slight withdrawal of alkalies from the blood.

The acid amids, foramid, $CHO.NH_2$, and acetamid, CH_3-$CONH_2$-exert no such effect as would be expected, as Schultzer and Nencki[41] found that the acid amids are not changed in the body.

Having established that amido acids, the lowest cleavage products of protein decomposition, offer immunity against acidosis, Eppinger tried the effect of polypeptids—glyzylglycin and leucylglycin—which only retarded the death of the rabbit, while with pepton and gelatin the animal died very promptly from acidosis. This seems to prove to Eppinger's mind that the kind of food, and the way such food is utilized by the organism, is the primary condition in acidosis, and he thinks that diabetes may be an expression of disturbed proteid as well as of disturbed carbohydrate metabolism.

In a second paper Eppinger,[42] after reviewing the main substance of his first article, thinks that his experiments have some practical value in diabetes. After showing that the body derives the protective ammonia mainly from the food, he believes that the reason the organism succumbs to diabetic acidosis is because there is not enough protein food given to furnish the required amount of ammonia, and as the body is unable to furnish fixed alkalies for any length of time, acid intoxication is bound to follow. The gastrointestinal disturbances preceding may be due to a defective breaking down of protein, with the necessarily resulting diminution of ammonia. In coma, therefore, Eppinger recommends the use of urea subcutaneously, and amido acids per os and per rectum, although he is inclined to Ebstein's view, namely, that diabetes is more a disease of entire protoplasm which prevents the organism from using even amido acids (Mohr). Despite the apparent absurdity of giving a person substances which are not utilized, Eppinger, nevertheless, recommends trying amido acids, as he considers the treatment of coma futile in any case, and the amido acids can do no harm.

As Folin points out, "the alkali therapy must, after all, furnish the final practical proof of the validity of the acid intoxication theory," and this is true, to a certain extent, but it must be remembered that not all cases of diabetic coma are comparable. Some are seen early and some late in the course of the disease, and this must vitiate to a certain extent the results obtained with the alkali treatment. Remembering the work of Busse,[26] the destructive changes wrought by β-oxybutyric acid must be borne in mind, and if, as Ebstein (quoted by Eppinger) states, diabetes

41. Hammarsten. Physiol. Chem., 5th edition, p. 546.
42. Ztschr. f. exper. Path. p. Therap., 1906, p. 530.

is a disease of the entire body protoplasm, it will be seen that when destructive changes take place in the body just how futile any treatment must be. That early cases of coma are benefited by alkaline remedies there can be no doubt, and even in the advanced cases improvement and sometimes postponement of lethal termination have been observed.

β-oxybutyric acid seems at present to be the cause of acidosis. Why this acid is formed is as much a riddle as ever before, and the glib answer that the body has, in a measure, lost its oxidative power is but a confession of our ignorance of the subject in question. All we know is that β-oxybutyric acid is seen in advanced diabetes, is seen in coma, has been found in excessive amounts in the organ tissues of diabetics dying in coma (Magnus Levy), and appears to be the cause of diabetic acidosis. The ever-recurring "But why" must be left for future investigators to answer. Theories there are, and many, but theories without proof remain but theories, and are to be adjudged as such.

SUMMARY AND CONCLUSIONS.

Together with a clear understanding of diabetic acidosis must be brought a knowledge of normal physiologic facts, which the foregoing, dealing only with the important publications of the past eight years, hardly touched on. It will be remembered that during the breaking down of carbohydrate, fats, and proteins numerous products of an acid nature are normally formed. These acid bodies are for the most part carbon-dioxid, sulphuric, hydrochloric and phosphoric acids, besides uric acid, fatty acids, and occasionally other acids. The carbon-dioxid is mostly excreted by the lungs and, in part, by the skin, while the sulphuric acid and other acids are excreted in the urine. These acids are, however, never found as such, but are combined with the body alkalies, forming salts. To neutralize these acids, the body must be deprived of its alkalies, and this loss is covered mostly by the alkalies contained in the ingested food. Besides these, however, the body contains a certain amount of "reserve alkali" which is found in the protoplasm of the body cells as potassium. The alkalies ingested with the food are found as sodium salts in the circulating blood, and to their presence is due the alkalinity of the blood. Besides these combinations of alkalies with inorganic acids, sodium phosphate and sodium carbonate are present, and these also help in preserving the blood alkalinity. The amount of these alkaline bodies is not great; 100 grams of blood contain a quantity equal to only about 180 mgr. of NaOH (v. Noorden).

If alkalies are being constantly withdrawn from the body by the intermediary products of tissue decomposition, it will readily be seen that

abnormal sapping of the alkali reserve can be accomplished by lessening the ingestion of alkalies in the food or by increasing the amount of the acid in the body. We have seen from Eppinger's work what fatal effect the administration of acids has on rabbits. Not only are there symptoms of acid intoxication, rapid respiration and increased pulse rate with convulsions, coma and death, but there is also an increase of the bases of the urine with a diminution of the blood alkalinity and of the carbon-dioxid from the lungs, indicating withdrawal from the body of alkalies. It will also be recalled what prompt beneficial effects follow the administration of alkalies. In dogs we have learned that, besides these labile and fixed alkalies of the body, there is a further protection offered by ammonia which is, for the most part, derived from the protein food. These teachings of Walther, Eppinger and others we have transferred to man, and we know that, thanks to our carniverous tastes, we are able to produce ammonia in such enormous amounts that our protection against even high acid values in the body is assured. Even under pathologic conditions, such as diabetic acidosis, v. Noorden reports that an output of ammonia from 4 to 6 grams a day is not at all uncommon, and Stadelmann once found 12 grams. When it is recalled that the normal output is between .3 and .7 grams, depending, of course, on the ingested food, and that each gram above that accounted for by the food corresponds to 6.12 grams β-oxybutyric acid, it will be seen what a great protection the ammonia is to us and what great quantities of acid it can neutralize.

The name acidosis was coined by Naunyn to cover the symptom-complex of the presence of increased acid in the body, and is, of course, always a sign of disturbed metabolism. This increase of acid can occur in two ways, deficient elimination and increased production. The first is relatively unimportant and never produces the symptoms of acid poisoning. The second is of prime importance, and may be associated with the former, when it is of double significance. The three acids with which this paper deals are β-oxybutyric acid, diacetic acid and aceton, called, for convenience, aceton bodies (Geelmuyden). Of these three, only aceton is seen normally in the urine, although some modern writers contend that this is not so, that aceton is never preformed, but is really diacetic acid. Until this matter is cleared up I prefer to regard the aceton determined by our qualitative tests, as aceton. That aceton is a product of normal metabolism can not be denied, and, though there is some doubt as to its toxicity, I believe it has been pretty definitely shown that aceton does not produce acidosis (Grube, Satta). Diacetic acid is also readily oxidized when given to healthy individuals, and we have seen from Lépine's experiments what large quantities of β-oxybutyric

acid a dog can take care of without showing symptoms of acid intoxication. What, then, causes the symptoms of acidosis and coma if the aceton bodies are so innocuous? The correct answer I believe to be is increase of acid in the organism. This acid might just as well be sulphuric acid or any other acid, if such could be formed in equally large amounts as β-oxybutyric acid, but it so happens that in diabetes β-oxybutyric acid is the cause. It must be insisted on that β-oxybutyric acid possesses no individual toxic properties not shown by other acids, but the deleterious effects ascribed to it are due to its purely acid character and, owing to its acid nature, it has the power of extracting from the body its alkalin supply and in this way producing acidosis.

The source of these aceton bodies now seems to be practically settled. That the principal source is from fat, especially fat containing fatty acids, can not be denied after the abundant proof offered. That the aceton bodies can be derived from protein has been shown by Blumenthal and Neuberg, also by Orgler, *in vitro,* but conclusive proof has been brought by Embden, Salomon and Schmidt, after finding increase of aceton after perfusion with leucin. That the formation of aceton from albumin takes place over fatty acids after denitrifying the amido acids is also a well-established fact, so that there should be no further controversy about the question whether aceton is derived from fat or proteid. Carbohydrates are not the source of aceton bodies.

The place of formation of aceton bodies is probably in the liver (Embden and Kalberlah, Embden, Salomon and Schmidt), although there are some supporters of the intestinal origin, especially J. Müller. Lüthje has found that acetonuria is not diminished by the use of laxatives and intestinal antiseptics, and v. Noorden has noticed even an increase following such measures, so this seems to disprove the enterogenous theory of aceton formation (Satta).

A CASE OF INFECTION WITH SCHISTOSOMA JAPONICUM IN A FILIPINO.

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For over twenty years physicians practicing in Japan have observed, in certain provinces, a peculiar cirrhosis of the liver with diarrhea, fever, anemia, ascites and edema. In some of these cases ova of an unknown parasite have been observed in the liver and other organs.

In the latter half of 1904 Katsurada[1] described ova found in the feces of patients and in the tissues of men and cats. He also described the adult worms as found in the portal and mesenteric veins in cats, and called the parasite *Schistosoma japonicum*.

Early in 1905 Catto[2] reported a case in a Chinaman from the province of Fukien. He described minutely the ova found in the tissues, and the parent worms found at the bifurcation of the smaller mesenteric vessels. Catto called the parasite *Schistosoma cattoi* (Blanchard). This case was previously published as one of coccidiosis in man, and again as one of infection with a new trematode.

Logan[3] has reported three cases in Chinese.

In January, 1906, Woolley[4] reported a case of infection with *Schistosoma japonicum* in a native Filipino, and so far as I know this was the first case reported from the Philippine Islands.

My case is that of a Filipino scout about 30 years old, who had been in the service of the United States about eight years.

Patient.—The man was born on the Island of Samar, was enlisted at Tagabian, Samar, and his company has been stationed there for some time. He had never been away from the Philippine Islands, and most of his life had been spent on the Island of Samar.

History.—The man was on furlough and entered the Division Hospital, Manila, P. I., at 10:00 a. m., January 16, 1908, in the service of Captain Ruffner, to whom I am indebted for all the clinical notes. The man complained of nothing but weakness and there was nothing in his appearance or on examination that would indicate that he was seriously ill. His temperature was 98.6 F., and his pulse 120. At 1:00 a. m. on January 17, the man began having diarrhea and severe

1. Jour. Trop. Med., London, 1905, viii, 108.
2. Jour. Trop. Med., London, 1905, viii, 70.
3. Jour. Trop. Med., London, 1906, ix, 294.
4. Philippine Jour. of Sci., January, 1906, p. 83.

abdominal cramps. He passed quickly into collapse and died at 6:45 a. m., January 17.

Autopsy.—As there was considerable cholera in Manila at the time we had at the autopsy to look out for cholera and beriberi.

General Appearance.—The body was that of a normally developed Filipino. There was no edema and no excess of fat was noted on opening the abdomen or about the abdominal viscera. There was no ascites.

Liver.—The liver appeared slightly enlarged, but about normal in color. The smooth surface was studded over with numerous yellowish spots from 1 to 1.5 mm. in diameter. The liver cut with increased resistance, the capsule was thickened, and the connective tissue about the gall bladder and along the larger bile ducts was markedly increased in amount, and was edematous and bile stained. The same yellowish nodules seen on the surface were dotted throughout the liver substance. Crushing the nodules showed them to contain a number of brown ova. The gall bladder was distended with thick bile, but the passage into the duodenum was free. Microscopically these miliary nodules have a caseous center and a fibrous margin with rather distinct line of demarcation from the liver tissue. They are usually connected with an area showing new formation of bile ducts. The general picture of the liver is that of a hypertrophic cirrhosis with new formation of bile ducts. Ova were found in some of the nodules; in masses in new formed connective tissue which shows new formation of bile ducts; and singly in the small vessels among the liver cells. In the latter position there is often no evidence of new formed connective tissue.

Intestines.—In the upper part of the rectum was an area, two inches long and extending half way around the rectum on the mesenteric side, in which the mucosa was swollen, red, and very slightly and superficially eroded. Otherwise the intestine and its contents appeared normal, except for a few uncinaria in the upper part of the small intestine. Cultures for comma bacillus were negative.

Microscopically the mucosa of the large intestine is normal, except for slight superficial erosion. The submucosa is thickened and there is considerable round celled infiltration. The muscularis is normal as is the subperitoneal tissue. Ova are found in fair numbers in the submucosa in areas of round celled infiltration. No ova are found in the other layers. Microscopically the small intestine shows nothing abnormal.

Kidneys and Suprarenals.—There was a yellowish nodule 2 mm. in diameter, 3 mm. from the base of one of the pyramids of the right kidney. Microscopically, this nodule is composed of fibrous tissue with a few remains of the kidney tubules. Otherwise the kidneys appear normal. No ova are found in this nodule or any where in the kidney tissue. There were two yellowish nodules, 1 mm. in diameter, bulging above the surface of the right suprarenal gland. Microscopically, both of these nodules are composed of fibrous tissue. Otherwise the suprarenals appear normal. No ova are found in these nodules or anywhere in the suprarenals.

Lungs.—The lungs showed nothing but slight congestion. Microscopically, there is considerable round-celled infiltration in the alveolar walls, and some ova are found lying singly in the areas of infiltration.

The brain, thyroid, pancreas, bladder and prostate appear normal.

The spleen was somewhat enlarged, dark colored and bloody.

The mesentery showed nothing. The vessels were carefully slit up but no worms were found, and none have been found in sections of the mesentery.

Heart.—The heart was pale and flabby and I was inclined to think that the man had died of beriberi, but sections from the tibial nerves showed nothing abnormal. Katsurada says: "A certain number of the patients die of extreme weakness," and that is all that I can find to account for the death in this case.

It is possible that the worms form a toxin, as suggested by Katsurada, and that this toxin had something to do with the sudden death in this case.

Bacteriologic Examination.—Sections from the nodules in the liver, kidney and suprarenal were stained for tubercle bacilli and for spirochetes, but neither has been found. The ova found correspond in appearance and measurements with the ova of *Schistosoma japonicum*.

This case is of interest, as there were present practically no other parasites and no lesions other than those due to the schistosoma, and those lesions were of the nature of a fibrosis.

Whether or not the nodules in the kidney and suprarenals were caused in any way by the schistosoma I can not say. I find no mention of lesions in the kidneys or suprarenals, and Catto says: "The kidneys, suprarenals, . . . showed no signs of coarse disease."

THE TREATMENT OF GONOCOCCUS ARTHRITIS BY INJECTIONS OF DEAD GONOCOCCI, AND THE CLINICAL REACTION WHICH FOLLOWS THE INJECTIONS.*

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Relatively few cases of gonococcus arthritis and periostitis treated by the subcutaneous injection of dead gonococci have so far been recorded. Cole and Meakins[1] reported fifteen cases of gonococcus arthritis in which inoculations were given and systematic observations made on the opsonic index. After a careful study of the cases they concluded that inoculation of dead gonococci appeared to have a decided value in favorably influencing the course of the disease.

This paper is based on the study of forty cases of gonococcus infection, including thirty-one cases of arthritis.[2] The diagnosis of each case included in the series was determined beyond any reasonable doubt, from the clinical history and course as well as from the associated genital infection. In all the cases in any way obscure the diagnosis was confirmed by the isolation of the gonococcus from the joints, and in two cases from the blood.

In fifteen of the forty cases studied the opsonic index was systematically determined. The initial indices were usually low, with rises following injections of dead gonococci. Aside from the injections of dead cocci, other factors, such as massage of the prostate and massage of affected joints, were found to raise the index. This has been observed also by Wright and others. Furthermore, spontaneous fluctuations in the index occurred in untreated cases of arthritis, due possibly to trauma or movement of an acutely inflamed joint.

Taking these facts into consideration, and bearing in mind that the opsonic curve is the expression of only one of the many changes which

*Read before the Chicago Pathological Society, March 9, 1908.

1. Treatment of Gonorrheal Arthritis by Vaccines, Bull. Johns Hopkins Hosp., xviii, No. 1905, June, 1907.

2. The histories of these cases, with details, will be found in a more complete paper to appear in the Journal of Infectious Diseases, vol. v, No. 3.

may take place in the body fluids in the course of infections, and that for some time at least inoculation therapy will depend for its control largely on clinical observation, it seemed advisable in the present work to use the clinical manifestations as the guide to the size and interval of the injections.

The lesions that occur in the course of generalized gonococcus infections present certain characteristics that render these cases peculiarly favorable for the observation of the clinical effects of therapeutic injections of dead cultures of gonococci. The course, even in the acute cases, extends over a number of days at least, and much more often over weeks and months. The fever and other constitutional disturbances are relatively less than in other infections of corresponding extent in the body, and the lesions, involving chiefly the joints, tendons and periosteum, are readily accessible to examination and careful observation.

In order that the inoculation treatment may have a general practical clinical value in the event of the experimental results receiving further confirmation, the dead cultures must be prepared, at least for the present, from heterologous organisms, for in many cases it is not only impracticable but impossible to obtain the so-called homologous strain.

Accordingly, for the purpose of uniformity, all the cases in this series were treated with cultures obtained from other sources than the patients in question. The cultures of the gonococcus used were isolated from various lesions, including urethritis and arthritis.

To obviate, in part at least, certain objections to the use of heterologous organisms, some of the material was prepared from two and sometimes three strains of the gonococcus. In many cases, however, but one strain was used. In a clinical study of this nature it is a matter of extreme difficulty adequately to compare the results with different kinds of killed gonococci. The general impression is that the immunizing responses were as good when one strain was used as when two or three were combined.

In the early cases treated, from 20,000,000 to 50,000,000 organisms were given at a dose. A dose of this size usually produced a rise in the opsonic index, but often no coincident change occurred in the clinical course of the disease. It seemed advisable to increase the dose, and accordingly in the later work from 100,000,000 to 1,000,000,000 organisms were given. The intervals between injections varied from three to seven days.

THE GONOCOCCUS REACTION.

In following the clinical course of the cases under inoculation treatment daily records of both subjective and objective conditions were made in so far as this was possible. It soon became evident that the course of events following the inoculation was not always one of progressive improvement. When seen twenty-four hours after the injection, patients repeatedly complained that the joint pains were worse rather than better. At this period of the work the dose used was relatively small, and the exacerbation of the symptoms did not occur regularly after each injection, so that for a time the phenomenon was regarded as an accidental coincidence. When the initial dose was increased, however, it was found that frequently the patients suffered from increased articular pain and tenderness after the first, often after the second, and occasionally after subsequent injections. Four cases in the same ward were given their first injections on the same day, the dose being 500,000,000. On the following day two of the cases showed only a slight increase in symptoms, with some rise in temperature and pain in the joints. In these two the arthritis was not extensive. In the other two cases in which the joint involvement was greater there was a decided exacerbation of symptoms. The involved joints became more acutely tender, and the fever which had previously not exceeded 99.5° F. rose to 101.5°, associated with general malaise. On the second day after the injections the acute symptoms had subsided and the patients felt about as well as before the injections were given. During the succeeding days improvement was more rapid than before the injections, so that the net gain of the first week of treatment was greater than that of the week preceding. In these cases the clinical picture after injection was most striking, and was highly suggestive of the phenomena observed in the tuberculin reaction.

The clinical records of the cases treated before this observation was made were now examined, and in those in which daily records had been made it appeared that the characteristic reaction had occurred, though by no means to so great a degree. In subsequent cases it usually has been possible so to graduate the dose of gonococci as to produce the reaction.

A typical gonococcus reaction is characterized by a rise in temperature, often only slight, an increase in pain and tenderness in the affected joints, with occasionally some increase in swelling and a variable degree of malaise. The symptoms follow the injection in from eight to twelve hours and commonly last twenty-four hours. In some instances there

is, too, a local reaction at the site of injection with tenderness, occasionally redness and some edema. These local signs commonly subside in twenty-four hours, though in three cases they persisted for three or four days. Great care has been taken throughout to insure surgical cleanliness in giving the injections. Moreover, in a number of normal individuals, to whom the same amount was given, no local reaction was noted. Leucocyte counts were made before and after the injections in a number of the gonococcus cases. Generally there was an increase in the leucocytes eighteen hours after the injections, though this was not constant. The degree of the reaction is influenced by several factors. After small doses (20,000,000 to 50,000,000 in the cases in question) the reaction was not marked, and in a number of the early cases treated it either did not occur or at least was overlooked. In one case (Case 1), however, in which a 50,000,000 dose was given, there was a reaction after each of the first three injections. When, beginning with a small dose, gradually increasing doses were employed, the reaction did not appear so typically, or was scarcely observable. When in a given case the same moderately large dose (300,000,000 to 500,000,000) was used for all the injections, the reactions became less with each injection. In four instances the reactions followed the initial dose only.

The most constant feature of the reaction is the increase in joint pain and tenderness. The temperature rise may be so slight as of itself to excite but little remark, especially in those cases in which there is a daily temperature of 99.5 to 100. In opsonic terminology the clinical reaction corresponds to the negative phase.

THE CLINICAL GONOCOCCUS REACTION IN DIAGNOSIS.

The frequency with which these clinical phenomena occurred suggested the possibility of utilizing the reaction in the diagnosis of obscure cases of arthritis in which the gonococcus was the suspected cause. The effects of the injection of dead gonococci into patients not suffering from gonococcus infection were accordingly studied. Eight adults in whom there was no history or sign of gonococcus infection were given subcutaneous injections of 500,000,000 dead gonococci. In none of these was there any local change other than that following an ordinary hypodermic puncture, and no fever or constitutional disturbance was observed. In a case of pyorrhea alveolaris with subsequent general infection, and painful swellings over the extremities, there was no increase of fever or local symptoms following the injection. A case of gout with

active joint involvement showed no local nor general change after a dose of 500,000,000. Leucocytes before injection 13,200, eighteen hours after injection 13,000; temperature normal throughout. A case of articular rheumatism showed no reaction after 500,000,000. There was no increase in leucocytes and the temperature chart showed no abnormal variations. A case of acute arthritis with pericarditis was thought possibly gonococcal in origin. There was no reaction after a dose of 500,000,000. Cultures from the blood and from a small amount of clear fluid aspirated from the knee remained sterile and the prostatic fluid contained no gonococci. The subsequent course was typical of acute rheumatic fever. In four other cases of acute and subacute articular rheumatism there was no reaction after injections of 500,000,000 cocci.

In a number of suspected gonococcus cases the reaction was of value in making an early diagnosis. A case of monarticular arthritis with effusion in the knee in which gonorrheal infection was denied was given an injection of 500,000,000. The evening temperature, which had previously reached only 100, rose to 101.8 and the joint pains increased. The knee was aspirated and the gonococcus isolated in pure culture from the fluid. A case of chronic arthritis which had resisted all treatment was given an injection. A slight rise in temperature, with increase in joint pains, followed. The prostatic fluid was found to contain gonococci, and the subsequent course was that of gonococcus arthritis. A patient who had suffered from extensive gonococcus arthritis had been bedridden for one year. There was practically no motion in the knees. After an injection of 500,000,000 the temperature, which for weeks had been normal, rose to 99.5, and the patient complained of malaise and increased pain in the joints. A patient with aortic aneurism who denied gonorrheal infection had been selected for control experimental inoculation. After an injection of 500,000,000 cocci the temperature, which had been uniformly normal, rose to 100 F. without any other apparent cause, returning to normal next day, with no subsequent rise. The prostate was examined and found to be large, somewhat tender, and the secretion contained numbers of leucocytes with typical intracellular gonococci.

CLINICAL RESULTS.

The clinical course of gonococcus infections is extremely variable. The large majority of the arthritic cases recover spontaneously, though frequently convalescence is long and tedious and the patient may be partially disabled for months. It is obviously fallacious to draw conclusions

as to the value of a treatment from the observations of isolated cases, and even when a number of cases of a disease so variable in its course as gonococcus arthritis are grouped together one must be very guarded in the conclusions as to the rôle of the treatment in effecting a cure. In summarizing the results the previous duration of the arthritis, its course in the days or weeks immediately preceding treatment, and the rapidity of subsequent improvement are of greater clinical weight than the mere statement of the time required to effect a cure.

In general the inoculations gave better visible results in the chronic than in the acute cases. In several acute cases improvement was apparently more rapid immediately following the injections than before. But while the acute cases terminated favorably and without undue delay, it must be recognized that they might have done so without treatment, though possibly less rapidly. The evidence in favor of the inoculation treatment is stronger in the subacute and chronic cases. In a number of cases in which after a typical acute course there remained more or less indolent swelling and tenderness in one or more joints, after the first injections the signs of the infection subsided rapidly. A patient (Case 26) had had a typical gonococcus arthritis for ten weeks. For six weeks before inoculation there had been no improvement in spite of treatment by rest and medicines. He was able to hobble around, but the pain in the lower dorsal region, sternoclavicular joint and in the heels rendered him unable to work. After the slight reaction following the first injection of 300,000,000 cocci his pain was much less, and after two more injections at intervals of four days he was discharged with no pain or other disability. When seen two months later he was still free from the trouble. A number of similar cases might be cited.

The treatment of several very chronic cases was undertaken. A patient (Case 10) had suffered for years from recurrent attacks of "rheumatism" in the region of the lumbar spine and in the heels. For seven months, with the exception of one month, he had been unable to work. At one time the heels, at another the back seemed to be worse. He had taken medicines of many kinds, electrotherapy, etc., without benefit. The prostate was large, tender, and the fluid obtained by massage contained typical gonococci. Inoculation of dead gonococci was followed by an increase in pain and tenderness for twenty-four hours, and then by improvement. After six injections during a period of one month his condition was very much improved and he was able to go to work. Each injection was followed by an exacerbation of local tenderness. The sub-

sequent improvement was much slower but progressive. The injections were continued with increased dosage, combined later with massage of the prostate, which was much less tender than at the outset of treatment. At the end of three months' treatment recovery was practically complete. The later injections were not followed by any observable clinical reaction.

In four of the thirty-one cases in the arthritic series the results were unsatisfactory. Two of these (Cases 18 and 22) were acute cases in which but two injections were given because of peculiar obstacles to treatment. These might reasonably be omitted from the series. Another early but extensive case (Case 2) received only small doses (50,000,000) for one month without improvement, and the treatment was discontinued. Massage of the prostate was substituted, with subsequent recovery after a slow convalescence.

The fourth case was that of a chronic alcoholic, who had also a chronic nephritis with considerable edema. In addition to his gonococcus arthritis, he had an otitis media and a dacryocystitis of a year's duration. Occasionally a slight reaction could be obtained after inoculation, with temporary improvement, but he suffered repeated relapses, with the involvement of new joints, and the treatment was finally discontinued.

The general impression derived from a study of the series of cases individually and as a whole is that inoculation was of material value in hastening recovery. The evidence is strongest in the more chronic ambulatory cases in which the benefit of rest in bed can be eliminated.

Certain other general therapeutic measures also contributed to the favorable results. The repeated withdrawal of joint fluid in large recurring effusions was no doubt of value. Only the smallest degree of fixation of joints was used. There were no cases in which ankylosis occurred. Prostatic massage has long been recognized as a valuable measure in gonococcus arthritis. It is highly probable on clinical grounds as well as from its effect in raising the opsonic index that prostatic massage results in an autoinoculation similar in its effect to the injection of killed gonococci. In several cases in which, for purposes of observation of the unaided effects of inoculation, systematic massage of the prostate was omitted, the condition of the prostate improved coincidentally with the improvement in the arthritis after inoculation.

SUMMARY.

Systemic infections by the gonococcus tend to spontaneous recovery. In many of the cases of gonococcus arthritis the clinical manifestations

are acute and the course extends over a few days or weeks. Certain cases, however, do not recover so quickly and the condition passes into a chronic stage which may last months or years. In the first class of cases immunity develops rapidly, and clinically little benefit appears to result from the injections of dead gonococci. In the chronic cases the mechanism of immunity fails to rid the body of the organisms, and they persist either in the original lesions or in one or more foci, such as the prostate, and give rise from time to time to new lesions at various points of localization. When dead gonococci are injected a reaction frequently follows, with an increase in constitutional and local symptoms. The reaction is later followed by a period of improvement. The fact that with a dose of constant size the reactions become less with each injection would seem to be a strong argument in favor of the value of the injections in hastening the development of immunity. Clinically in a number of cases the injections of dead gonococci have seemed to be of distinct value.

Many more series of cases will have to be studied before a definite opinion can be expressed, but the results obtained thus far seem to indicate that in certain cases of gonococcus arthritis recovery can be hastened by the injection of dead gonococci. No harm has been seen to follow the injections, and it is possible that the use of larger doses will be found desirable in some cases.

With further work the limitations as well as the advantages of the method will appear, and it should be recognized that while it is attractive theoretically as a specific therapeutic measure, too much must not be expected of it in the way of marvelous cures. It should be used rather in conjunction with other general measures, such as rest, aspiration of joints distended with fluid, massage of the prostate and other surgical and general hygienic treatment.

The reliability of the clinical gonococcus reaction as a diagnostic procedure will also be determined only after many tests. It has many points in common with the tuberculin reaction, and similarly, too, there may well be cases of gonococcus infection found which do not respond. It appears, however, to be well worth a trial. Should the reaction prove to be reliable, a valuable and much needed aid will be at hand for the diagnosis of obscure joint, synovial and periosteal diseases.

Until recently it has not been deemed expedient to carry on experiments on certain other phenomena of hypersusceptibility in gonococcus infections such as the ophthalmic reaction, though this work has now been begun. It has already been noted that the local reaction after

the injection of dead gonococci is greater in cases of gonococcus infection than in normal individuals.

I am greatly indebted to Dr. Hektoen of the Memorial Institute for advice and guidance during the preparation of this paper, and to the attending and house staffs of the Presbyterian and Cook County Hospitals for the opportunity afforded to observe clinical cases and for assistance in carrying out the treatment. I wish also to acknowledge the valuable assistance of Drs. A. H. Curtis and R. C. Menzies of the County Hospital, who devoted much time and care to the daily observation and recording of the clinical phenomena of the cases in their charge.

103 State Street.

THE USE AND THE VALUE OF TUBERCULIN IN THE DIAGNOSIS OF PULMONARY TUBERCULOSIS.

LOUIS HAMMAN,
BALTIMORE.

In the last ten years the literature on the diagnostic use of tuberculin has been enriched by a large number of important and exhaustive contributions,[1] and we are now in a position to pass at least a temporary judgment on the value and the shortcomings of the method. After the first few years of extensive application of tuberculin following its introduction in 1890[2] its use in diagnosis was largely abandoned when in treatment it had proved not only valueless but harmful.[3] The tuberculin revival, in the midst of which we are at present, is an outcome of the modern sanitarium movement, the ever-increasing demand for earlier and earlier diagnosis being the motive and abundant material and convenience for careful observation the opportunity. Bridging the two periods is the work of a few such enthusiasts as Trudeau, Fraenkel, Spengler, Petruschky, Möller and others who kept interest alive and communicated it to their near associates. Dr. Trudeau's influence has always been strongly felt in Johns Hopkins Hospital, and tuberculin, while not extensively, still has been continuously employed for diagnosis during the past fifteen years.

For fourteen months we have used tuberculin rather largely in the Phipps Dispensary both in diagnosis and treatment, having made in round numbers about five thousand injections. Naturally we see a great many cases in which, after a careful application of the usual methods of diagnosis, doubt remains. In an effort to reach greater assurance we have turned to tuberculin, and I have analyzed the first 94 cases injected as a text for this paper. We have nothing new to repeat nor any startling modifications to suggest, but we have made a number of observations of great interest to us which may serve as illustrations to point a more reasonable attitude toward tuberculin. Prevalent misstatements about the best methods of use and the value of tuberculin in diagnosis might

1. Beck: Deutsch. med. Wchnschr., 1899, Nos. 5-9. Möller and Kayserling: Ztschr. f. Tuberk., 1902, iii, 279. Hammer: Beitr. z. Klin. d. Tuberk., 1903, i, 325. Löwenstein and Rappaport: Ztschr. f. Tuberk., 1904, v, 485. Bandelier: Beitr. z. Klin. d. Tuberk., 1904, ii, 285. Köhler: Tuberculin u. Organismus, Fischer, Jena, 1905. Roth-Schulz: Beitr. z. Klin. d. Tuberk., 1906, vi, 167. Roepke: Ztschr. f. Tuberk., 1907, x, 412. And many others.

2. Koch: Deutsch. med. Wchnschr.

3. Most important early literature on tuberculin may be found in Klinisches Jahrbuch, Ergänzungsband, 1891.

be offered as a justification. One of our most prominent American pediatrists has recently written about tuberculin and says that the dose for an infant or young child is from two to five milligrams. Such an unqualified statement, I believe, might be productive of much harmful misunderstanding; and that four milligrams may be followed by serious results a case he cites illustrates. One reads so frequently that all of the patients in a certain group either had tubercle bacilli in their sputum or reacted to tuberculin. The impression is conveyed that these two pieces of evidence are of equal value, which they by no means are; and one gets the further impression that a reaction to tuberculin absolutely settles a doubtful diagnosis, which it certainly does not. A German author,[4] speaking of suspicious cases, writes that "Koch's old tuberculin

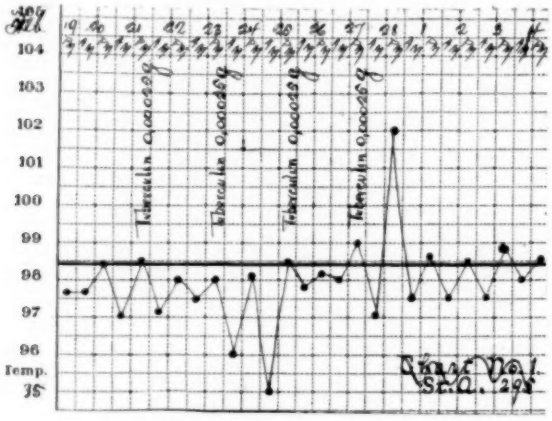

Chart No. 1.

is the sovereign means with which to establish the proper diagnosis with absolute certainty." Bandelier,[5] too, says that "the quintessence of tuberculin diagnosis is in the 'sicherstellung'—the making absolutely sure—of the diagnosis in doubtful cases." This term "sicherstellung" is frequently met in the German literature, and it is a matter of first importance to make quite clear how far its use is justified.

THEORETICAL CONSIDERATIONS.

There is no more interesting phenomenon in the whole range of medicine than the tuberculin reaction, and we are still far from a satis-

4. Ziegler: München. med. Wchnschr., 1907, p. 1320.
5. Beitr. z. Klin. d. Tuberk., 1904, ii, 285.

factory understanding of even its fundamental principles. Here is a substance, practically inert toward healthy animals, which under certain conditions becomes highly toxic toward subjects affected with even a trivial tuberculous lesion. A single focus of disease may so change every cell in the body that when a small amount of tuberculin is brought in contact with it a violent reaction ensues. A drop placed on a mucous membrane or rubbed into the skin or injected into the subcutaneous tissue produces extensive local changes. We know little about the nature of these changes. Since Wasserman and Bruck[6] have demonstrated the presence of antituberculin in the tissues and at times even in the blood we have come to view such changes as the expression of a specific reaction between the two substances, with perhaps a stimulation to the further production of antibodies. We are not yet sure that tuberculin itself causes this remarkable change in the body cells, for, desirable as such

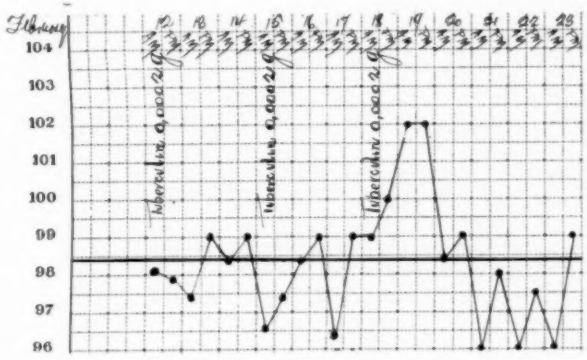

Chart No. 2.

information may be, it still remains to be proved that a normal animal can be rendered hypersensitive by the repeated injection of tuberculin. The fever and the constitutional symptoms are almost certainly due to a substance other than tuberculin, which is newly formed or produced in excess under the stimulation of the latter substance. The summation theory is no longer worthy of consideration. Wasserman believes that he has demonstrated the constant presence of antituberculin in tuberculous foci, and conceives that the tuberculin reaction consists in a local union of tuberculin and antituberculin, with the anchoring of comple-

6. Wasserman and Bruck: Deutsch. med. Wchnschr., 1906, No. 12. Wasserman and Bruck: Münch. med. Wchnschr., 1906, No. 49. Wasserman and Citron: Ztschr. f. Hyg., 1906, lii, 238.

ment, this new substance acting as a ferment on the tuberculous tissue and the absorption of the products of digestion causing fever and the characteristic constitutional symptoms. This is merely a new garb for the hypothesis which Ehrlich[7] advanced in 1900.

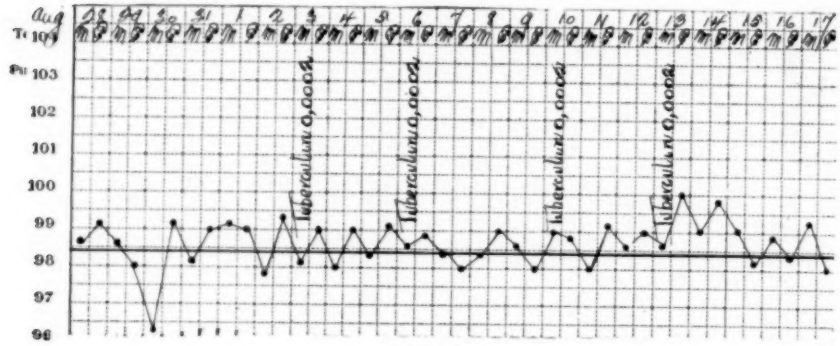

Chart No. 3.

In both of these hypotheses the presence of a tuberculous focus is an essential. Wasserman's views practically resolve themselves into a question of toxin and antitoxin, the absence of a reaction in a tuberculous patient being interpreted as a blocking off of the toxin from the tubercu-

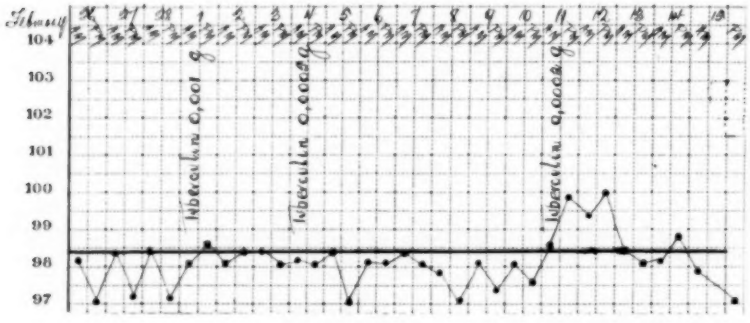

Chart No. 4.

lous tissue by neutralization in the blood stream. In some patients, particularly in those long treated with tuberculin, he has been able to demonstrate the presence of complement deviating substances in the blood, but

7. Internat. Kong. f. Hyg., 1900.

in only a very small proportion of cases. The work of Morgenroth,[8] however, and particularly the detailed considerations of Wolff-Eisner,[9] indicate that the conditions are not as simple as such a conception would

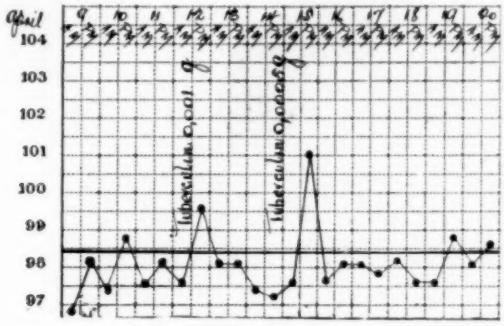

Chart No. 5.

lead us to believe. In the first place there is no evidence to show that the union of toxin and antitoxin ever gives a local reaction; then, too, all recent work on tuberculin demonstrates that its active agent is the al-

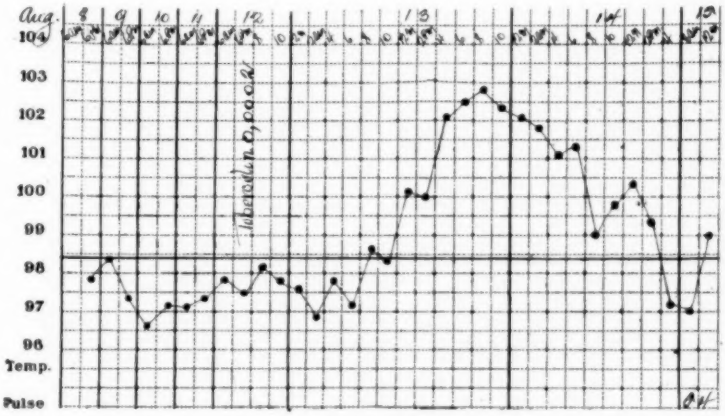

Chart No. 6.

buminous portion of the bacilli themselves which produces no antitoxin; further, a number of observations tend to show that reactions to tubercu-

8. Morgenroth and Rabinowitch: Deutsch. med. Wchnschr., 1907, No. 18.
9. Beitr. z. Klin. Tuberk., 1908, iv, No. 1.

lin may occur in the absence of tuberculous lesions, and, lastly, Wassermann's view fails to take into account the important principle of hypersusceptibility—perhaps better known under the terms allergie and anaphylaxis.

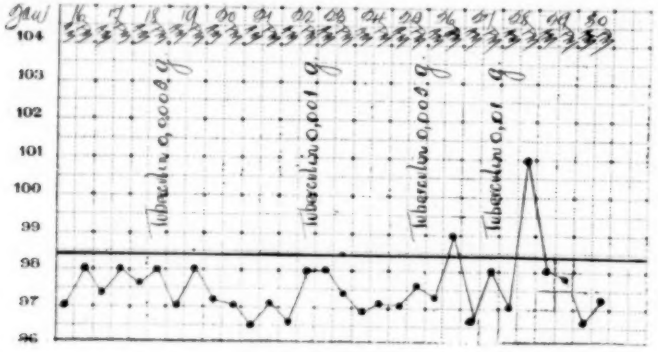

Chart No. 7.

Tuberculin differs according to the manner of its preparation. It is well known that many of the older preparations contained tubercle bacilli

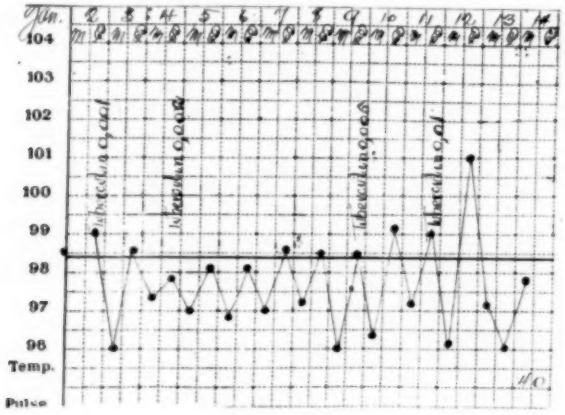

Chart No. 8.

in large number,[10] but if put through a Berkefeld filter no such gross particles are present. Nevertheless these two specimens will act in an

10. Wolff-Eisner: Beitr. z. Klin. d. Tuberk., 1908, ix, No. 1.

identical manner, displaying differences in degree, but never in the quality of reactions. Löwenstein[11] was first to draw attention to the development of hypersusceptibility to tuberculin in tuberculous patients. His instances and tables are conclusive, and the phenomenon has become the common observation of every one using tuberculin. This principle of hypersusceptibility is the fundamental symptom of the serum disease[12] and its production a property of all albuminous bodies. Preisich and Heim[13] were the first to demonstrate that animals who had no tuberculous lesion would react to tuberculin. In two instances they were successful in introducing into the peritoneal cavity of guinea-pigs capsules containing tubercle bacilli, and the animals soon acquired tuberculin hypersensitiveness, showing at autopsy no tuberculous lesions. Walle[14] and Maussu[15] report similar observations.

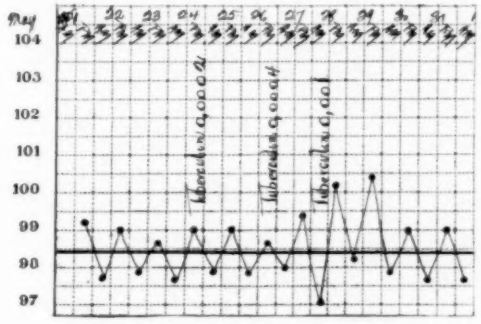

Chart No. 9.

The views of Wolff-Eisner seem to fit best into what we at present know of the tuberculin reaction and, shorn of their technicality, are briefly this: Tuberculin, which really consists of ultramicroscopic portions of the tubercle bacillus, produces the same effects in the animal body as tubercle bacilli, except that the latter are capable of multiplication. The local tuberculin reaction is caused by an accumulation of lymphoid cells, and true giant cells are formed. The injection of living tubercle bacilli is followed by the development of hypersensitiveness the same as that which follows tuberculin injections. As in typhoid and

11. Löwenstein and Rappaport: Ztschr. f. Tuberk., 1904, v, 285. Anderson: Hygienic Laboratory Bulletin, No. 26, 1907.
12. von Pirquet and Schick: Die Serumkrankheit, Vienna, 1905. Rosenau and
13. Centralbl. f. Bakteriol., 1902, p. 712.
14. Compt.-rend. Soc. de biol., lxi, No. 28.
15. Semaine méd., 1907, No. 49.

cholera, the immunity reaction in tuberculosis depends on the presence of lysins. The tuberculin reaction is not due to the tuberculin itself nor to the disintegration at the site of disease, but to a new toxic substance formed by the action of the lysins on the albuminous portion of the bacillary body. For this toxic substance to become active the organism must be in a condition of hypersensitiveness. There are, then, two factors to be considered: the presence of lysins and the condition of hypersusceptibility. The lysins may be artificially increased and are the bodies which deviate complement in Wasserman's experiment. The hypersensitiveness varies under conditions of which we are still ignorant, but it, too, may to some extent be stimulated or obtused. Normally there is no lysin present, or so small an amount that when tuberculin is injected the transformation goes on so slowly that the newly formed toxin causes no appreciable effect. Under continuous minimal stimula-

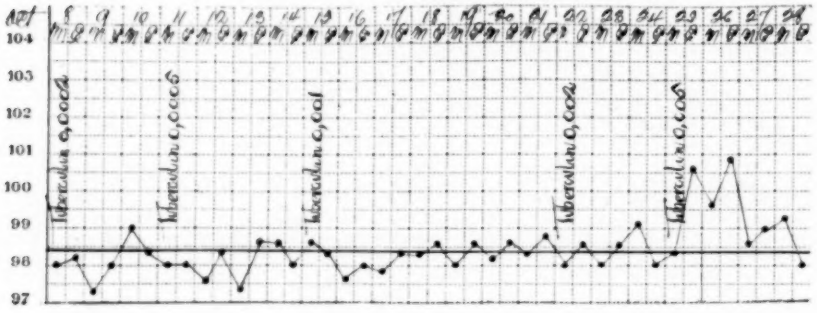

Chart No. 10.

tion the quantity of lysin increases, and the transformation then occurs so rapidly that after an injection intense toxic symptoms occur. The toxin causes a local reaction at the site of injection, constitutional symptoms and an inflammatory reaction at the site of the tuberculous lesion. During the inoculation of small doses of tuberculin hypersensitiveness is developed. Variation in susceptibility to tuberculin in tuberculous subjects depends essentially on variation in hypersensitiveness, lysins probably being present in all.

These theoretical considerations are of great importance for a proper appreciation of the clinical significance of the tuberculin reaction. They are the basis of a reasonable understanding of the question why many healthy individuals react and why some tuberculous subjects do not and give the foundation to our present method of conducting the reaction. Any number of instances of developing hypersensitiveness might be pre-

sented. Charts Nos. 1, 2 and 3 are examples. In all of them the repetition of a small dose has finally liberated a reaction. We can no longer even consider the explanation that Bondelier urges that these reactions are the expression of a summation. Löwenstein disposes of such a view in his original communication. The hypersensitiveness following tuberculin administration may last for a year. Not only can we get a reaction by repeating the same small dose, but occasionally the hypersensitiveness develops in a most striking manner with decreasing doses. Such a reaction is uncommon, but we have two illustrations. In Chart 4 the reaction is seen to follow 1/5 mg. after 1 mg. and ½ mg. were negative. In Chart 5 there is seen a marked reaction to ½ mg. after a slight reaction to 1 mg.

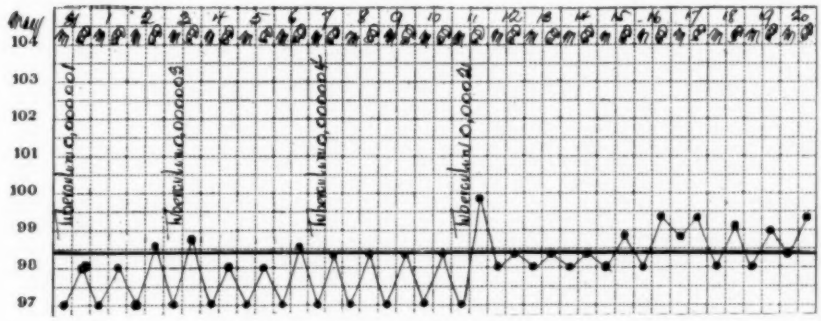

Chart No. 11.

THE SIGNIFICANCE OF TUBERCULIN HYPERSENSITIVENESS.

We know that many healthy individuals are unaffected by as much as 50 mg. of tuberculin. What is the significance of this marked sensitiveness to the reagent? There are two standpoints from which we may consider the specificity of tuberculin: First, will only those individuals who are affected with tuberculosis react, and, second, will tuberculous individuals react only to tuberculin, or will other substances produce the same effect? Our theoretical considerations, if they are valid, would certainly answer the first question in the affirmative, and we have a large statistical material from which to judge of practical results. In all such tests autopsy can alone be the deciding evidence. Naturally in man such control is impossible, but the extensive application of tuberculin to veterinary practice has given us the desired opportunity. Fraenkel[16] has

16. Ztschr. f. Tuberk., i, No. 4.

collected 8,000 observations on cattle, and the results of the tuberculin reaction have coincided with the autopsy findings in all but a little over 2 per cent. Voges,[17] in 7,327 observations, found a percentage error of 2.7. Nocard,[18] in 124 instances, found only one that did not coincide. Bang[19] has reviewed the question extensively and points out two sources of error. A certain number of cattle react in whom at autopsy no tuberculous lesion is found. Such an occurrence is uncommon and decreases in frequency in inverse proportion with the care exercised in searching for the lesion. It is no matter for wonder that a few tubercles no larger than the head of a pin will occasionally be overlooked. These animal observations impress on us particularly how very slight, indeed, a tuberculous lesion may be that has produced hypersensitiveness. A more important source of disagreement between test and autopsy is the not infrequent failure of a manifestly tuberculous animal to react. Such an oc-

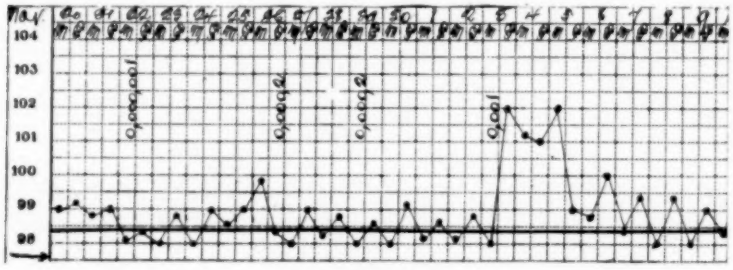

Chart No. 12.

currence is well appreciated in the study of human tuberculosis and would not enter as a disturbing factor in the clinical use of tuberculin.

It may seem trivial now to stop to consider the second viewpoint of tuberculin specificity, but it has played an important rôle in the history of its use. Rosenbach suggested when tuberculin was first introduced that the reaction depended on the instability of the heat-regulating mechanism of tuberculous patients and could be produced as well by numerous other bacterial poisons. Tuberculin, he contended, would cause fever in convalescents and patients in a "weakened condition" as readily as in the tuberculous. Matthes,[20] in 1894, investigated the effects

17. Ztschr. f. Krankenpfl., 1904, xxvi, Nos. 5-8.
18. Nocard, cit. Köhler: Tuberculin u. Organisms, Fischer, Jena, 1905.
19. Tuberculosis, Leipsic, iii, No. 5.
20. Deutsch. Arch. f. klin. Med., 1894.

of albumoses on tuberculous patients and, finding their injection produced reactions, suggested using solutions of these instead of tuberculin for the test. His work is still of great interest, indicating that the tuberculin reaction is chemically perhaps a group reaction, all albumoses being effective, but the specific albumose of the tubercle bacillus in far smaller doses than any other. The serum of Hayem, a 0.7 per cent. salt solution, at one time threatened to destroy belief in the specificity of tuberculin. Hutinel,[21] in an elaborate series of experiments, concluded that results with its use were as satisfactory as with tuberculin and that it was to be preferred on account of its harmlessness. Combemale and Mauton,[22] however, after extensive observation, showed the fallacy of Hutinel's conclusions. We can very safely say that tuberculin hypersensitiveness depends on the presence in the body of certain specific

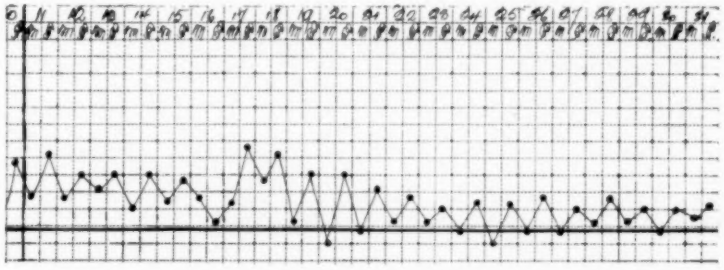

Chart No. 12—Continued.

substances which can arise only through intimate association with the tubercle bacillus and that the reaction is more than an expression of thermal instability.

THE CLINICAL FEATURES OF THE TUBERCULIN REACTION.

We may refer very briefly to our methods of observation, as they are those in general use. Fifteen of our cases received their injections at Eudowood Sanitarium, 43 at St. Agnes Hospital and 36 were treated as ambulant cases in the Dispensary.[23] In institutions the method of control is very simple. After at least one, and usually more careful exami-

21. Semaine méd., 1895, p. 117.

22. Cong. de méd. interne, Lille, 1899.

23. I am indebted for help in the observation of our patients particularly to Drs. S. Wolman, assistant in the Phipps Dispensary; A. M. Forster, resident physician Eudowood Sanitarium, and H. H. Hazen, resident physician, St. Agnes Hospital.

nation the patient's temperature is recorded, and if not above 99 for two days injections are begun. During the test period the temperature is taken every two hours. After each injection the patient's symptoms are recorded and the chest examined. As a rule, injections are given every second day, but at times a longer interval is allowed to elapse. Where time was pressing we have given some injections even when the temperature had previously been a little over 99, but this practice clouds the results and should be condemned. The ambulant patients were taught to record their own temperature and pulse rate and to keep a daily record of their symptoms. If after an injection their temperature goes to 99.4 or over, they report at the dispensary the following morning for examination, or if they are too ill they are visited at their homes. Injections are given twice a week. The method has proved very satisfactory, indeed, and we are making more and more of our observations in the dispensary instead of transfering the patients to a hospital.

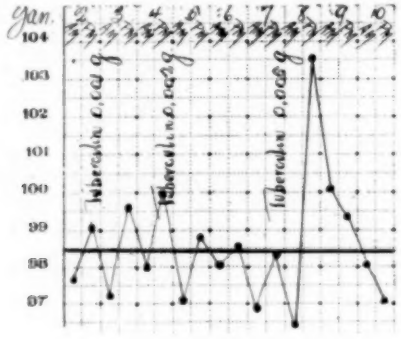

Chart No. 13.

In every tuberculin reaction there are four essential features which are the object of careful clinical observation: the temperature, the constitutional symptoms, the local reaction and the focal reaction.

When a patient reacts to tuberculin the temperature, as a rule, begins to rise in 6 to 12 hours, reaches its height in 12 to 24, and is normal again in 24 to 36. Unfortunately in analyzing our histories the length of time between the injection and the beginning of the rise was noted in only nineteen as follows:

In 10 instances, less than six hours.
In 6 instances, between six and twelve hours.
In 3 instances, between twelve and twenty-four hours.

It is uncommon for the reaction to be delayed over 24 hours, but Dr. Wolman has given me the notes of a case in which the temperature did

not begin to rise until 36 hours after the injection. In 64 observations the time between the injection and the height of the reaction was as follows:

In 2 cases, less than six hours.
In 14 cases, between six and twelve hours.
In 38 cases, between twelve and twenty-four hours.
In ten cases, over twenty-four hours.

The longest time was 36 hours and the shortest four. The duration of the reaction was as follows:

In 9 cases, less than twelve hours.
In 19 cases, between twelve and twenty-four hours.
In 25 cases, between twenty-four and forty-eight hours.
In 11 cases, over forty-eight hours.

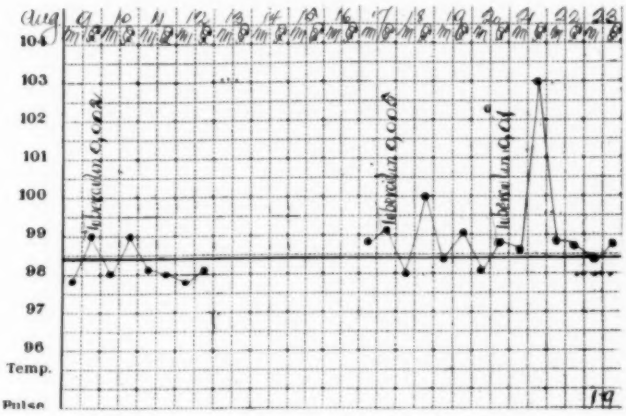

Chart No. 14.

The longest durations were ten days, over one week and three weeks.

It is of interest to know if the duration and severity of a reaction bear any relation to the size of the dose which liberates it. Such figures would be of value, if the reactions always occurred at the first injection, if we had any method of estimating how large such a dose should be. As it is, we must grope about in the dark until we find the proper dose, and in our experimentation the susceptibility of a patient may be greatly altered. To give 1 mg. after having given a few fifths is quite different from starting with 1 mg.

In 9 cases with a duration less than 12 hours, the liberating dose was under 1 mg. in 3 cases and 1 mg. or over in 6 cases.

In the 19 cases with a duration between 12 and 24 hours, the liberating dose was under 1 mg. in 5 cases and 1 mg. or over in 14 cases.

In the 25 cases with a duration between 24 and 48 hours the liberating dose was under 1 mg. in 5 cases and 1 mg. or over in 20 cases.

In the 11 cases with a duration of 48 hours or over, the liberating dose was under 1 mg. in 3 cases and 1 mg. or over in 8 cases.

By transposing these results we have the following: Of 16 cases reacting to doses under 1 mg., in 8 the duration of the reaction was less than 24 hours; in 8 the duration was over 24 hours. Of 48 cases reacting to doses of 1 mg. or over, in 20 the duration of the reaction was less than 24 hours; in 28 the duration was over 24 hours.

Certainly there is no striking difference in the duration of the reaction after large or small doses. According to the height which the temperature reaches, we may divide our cases into three groups: mild reac-

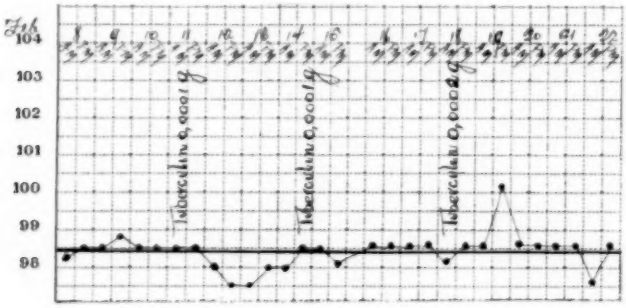

Chart No. 15.

tions in which the temperature remains under 100; moderate reactions, between 100 and 102; severe reactions, over 102.

Of 23 cases reacting to doses under 1 mg., 6 gave a severe reaction, 12 gave a moderate reaction, and 5 gave a mild reaction.

Of 53 cases reacting to doses of 1 mg. or over, 20 gave a severe reaction, 29 gave a moderate reaction, and 4 gave a mild reaction.

There is a higher percentage of severe reactions to the larger than to the smaller dose. Hammer, from an analysis of 180 cases, concludes that duration and severity of a reaction bear no relation to the size of the dose. In his series, however, he begins with 1 mg.

As our figures show, the usual type of temperature curve in a tuberculin reaction is a gradual rise to the high point and gradual fall to the normal as seen in the characteristic Chart 6.

Occasionally the temperature rises abruptly, at times the onset being marked by a chill so that only a few hours may elapse between the beginning of the rise and the fastigium as in Chart 7. The fall may be as abrupt as the rise, the whole reaction being over in four to six hours,

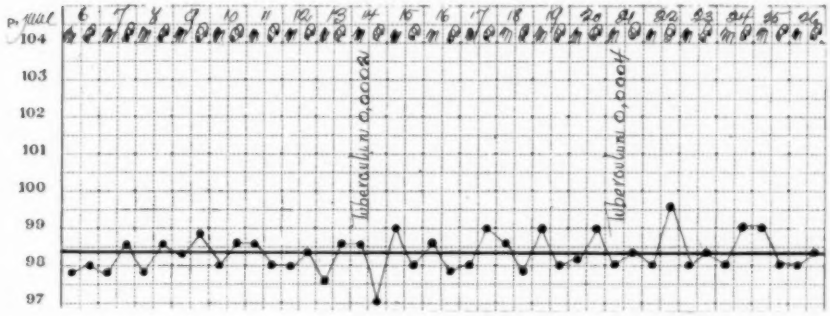

Chart No. 16.

as in Chart 8. Not infrequently the first elevation is followed by a secondary rise, as in Chart 9. Chart 10 is a good example of a sustained reaction. Of special importance are the cases in which the reaction is followed by a continued elevation of temperature for days or even weeks, as in Charts 11 and 12.

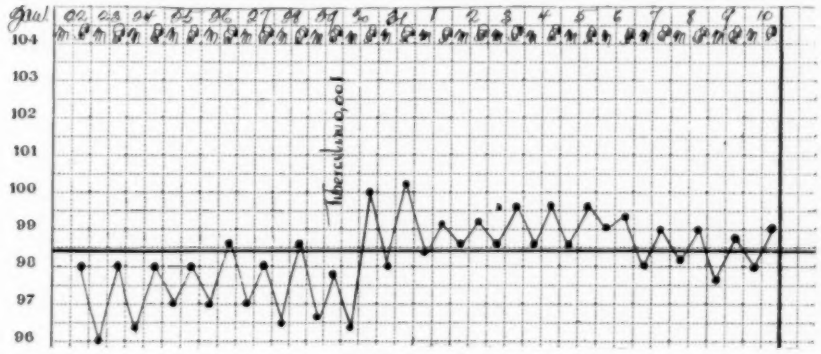

Chart No. 17.

The constitutional symptoms are as varied in character and in intensity as the temperature curve. They begin with the onset of the fever, reach the maximum at its highest point and gradually subside. When the temperature reaches normal the patient feels well again, except after

unusually severe reactions, when prostration and malaise may persist for days. The severity of the symptoms and the height of the fever bear no constant relation, however; indeed, the two seem often to be quite independent of one another. In many cases, as those shown in Charts 13 and 14, the constitutional symptoms are very slight, though the temperature reaction is over 102, while in others, as in cases shown in Charts 15 and 16, the constitutional symptoms are intense, though the temperature does not go over 100.

In the 17 cases with no marked constitutional symptoms:

3 had a slight febrile reaction.
10 had a moderate febrile reaction.
4 had a severe febrile reaction.

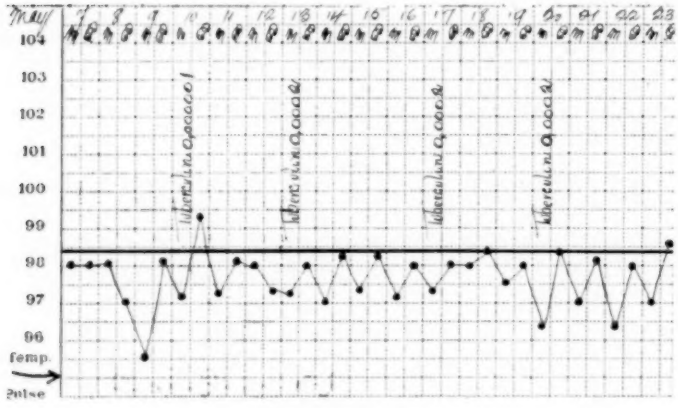

Chart No. 18.

In 43 cases with well-marked constitutional symptoms:

3 had a slight febrile reaction.
25 had a moderate febrile reaction.
15 had a severe febrile reaction.

In 14 cases with intense constitutional symptoms:

3 had a slight febrile reaction.
5 had a moderate febrile reaction.
6 had a severe febrile reaction.

I have made no attempt to analyze the various symptoms which arise and their frequency. This has been done in a thorough manner by Hammer. In typical cases patients invariably compare their symptoms to those of grippe. There is marked prostration, headache, intense pain in all the joints and limbs, and frequently nausea and vomiting. These symptoms may at times become alarming. No. 17 is the chart of a

patient, with a suggestive history and indefinite physical signs, who received an initial dose of 1 mg. Although the temperature rose only to 100.2, she became extremely ill. Almost incessant vomiting for three days with severe abdominal pain so prostrated her that the attendants and even the resident physician were seriously concerned about her safety. She recovered completely, however, and to all appearances suffered no permanent ill effects. Two of our cases became delirious; one, an epileptic, had a convulsion at the height of the reaction; two cases had an extensive eruption of herpes, and one unilateral sweating on the side of the injection. It is remarkable how frequently constitutional symptoms are present without a rise in temperature. For instance, the patient whose case is represented in Chart 18 received four injections of 1/5 mg.,

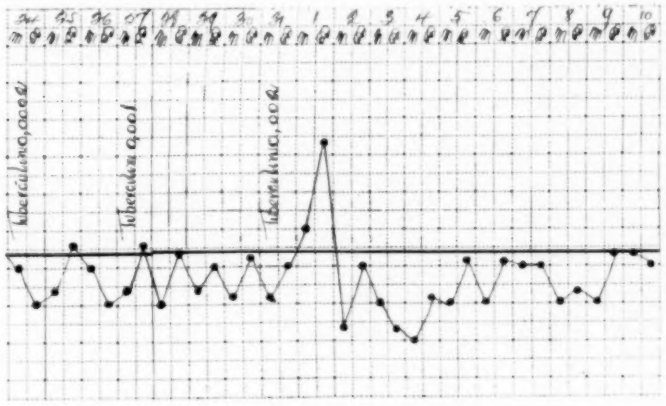

Chart No. 18—Continued.

then 1 mg. and then 2 mg. After the first dose she complained of general malaise and prostration, and after 1 mg. was quite ill. There is, however, no elevation of temperature until 2 mg. are given. It is common to have patients say, "Each one of these injections makes me very sick, but I have no fever."

The local reaction at the site of injection consists in redness, swelling and pain. The regional glands, too, are often swollen and tender. Unfortunately, its presence or absence has not been regularly noted in our records, but I can recall no single instance in which a patient reacted and it was absent. It may not be present after the particular dose which liberates a reaction, but when it is absent then it has been well marked after previous injections. Even more frequently than the constitutional

symptoms it is a forerunner of the coming reaction. It is almost the rule for patients to complain of pain and swelling after the doses preceding the one that gives a reaction. At times the local phenomena with the accompanying glandular swelling are the most prominent features in the reaction. Even with slight fever and almost negligible constitutional symptoms, a tumor as large as one's fist may arise at the point of injection. Curiously, too, a patient may show such a local reaction and never give either a rise of temperature or complain of constitutional symptoms even after much larger doses. We have two such instances. The patient whose case is shown in Chart 19 received four doses of 1/5 mg., one each of ½ mg., 2 mg. and 10 mg. After the first dose the temperature rose to 99.4 and there was marked pain and swelling at the site of the injection. After the second dose there was no rise of tem-

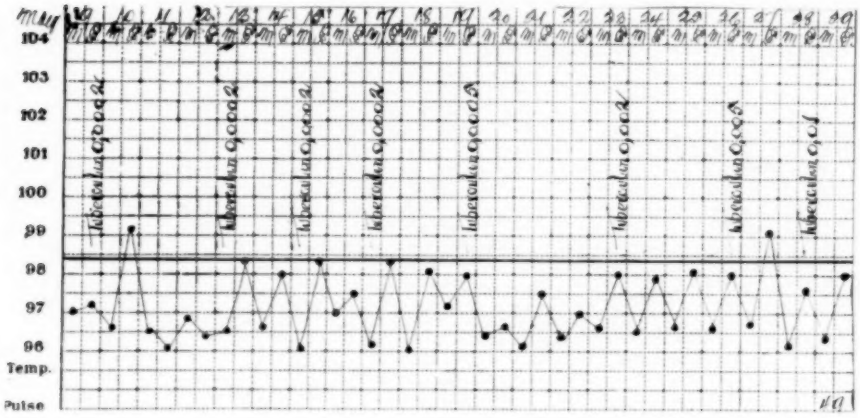

Chart No. 19.

perature and the local reaction was slight. From then on there was neither local nor febrile reaction, except that after 5 mg. the temperature went to 99.2. The patient never complained of constitutional symptoms. In the case shown in Chart 20 there was a marked local reaction after the first two injections.

When a tuberculous lesion is situated externally very remarkable changes are seen to occur during a tuberculin reaction. The focus becomes swollen and red and moist, and if the inflammatory reaction is severe it is followed by necrosis and sloughing. If the lesion is in the lung, evidence of such a reaction may be obtained from the symptoms and from physical examination. The characteristic symptoms are pain

in the chest and increased cough and expectoration. Occasionally there is hemoptysis, and tubercle bacilli, absent before, may appear in the sputum for the first time. In the case shown in Chart 21, with indefinite pulmonary signs, four sputum examinations were negative before the reaction; the fifth, immediately after, positive. In the case shown in Chart 22 several examinations before the reaction were negative; the one immediately after, positive. Möller reports similar observations in 4 of 123 cases. Our 2 instances occurred among 63 suspected cases that reacted. Fraenkel,[24] in 167 cases, found none that showed tubercle bacilli in the sputum after the reaction where they had been absent before. Hammer observed it once in 164 reactions.

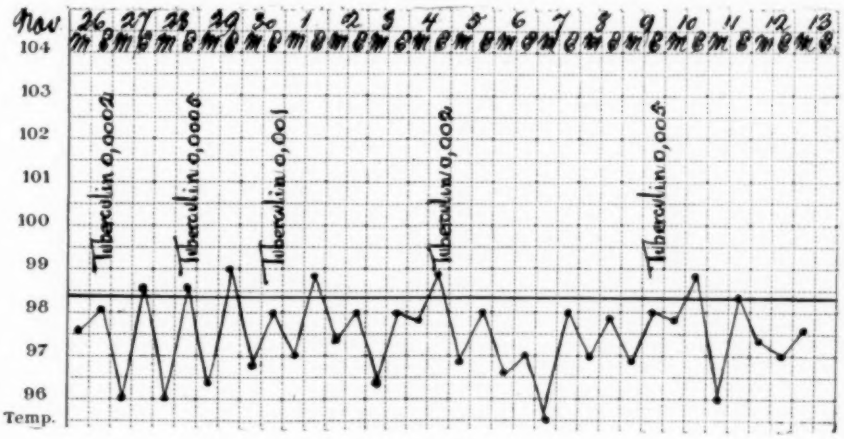

Chart No. 20.

Symptoms of a focal reaction in the lungs are not uncommon. In 60 doubtful cases that reacted, they were noted in 18 and marked as definitely absent in 17. In the remaining 25 cases no note is made about the condition, which means in practically all of the cases that the symptoms were not present. Of the 18 cases, 10 complained of increased cough, and 4 of these of increased sputum; 9 complained of pain in the chest. Of 13 cases with definite signs of a pulmonary lesion, 8 gave definite focal symptoms, and in only one the note is made that they were absent.

The physical signs of a focal reaction in the lung consist of changes in the character of the breath sounds and the increase or fresh appear-

24. Fraenkel: Lehr. d. Path. u. Ther. d. Lungenkrankheiten.

ance of râles. The frequency with which such signs are discovered will depend largely on the standard one sets. Roepke found them in 45 per cent. of his cases, but changes in the intensity of the breath sounds or

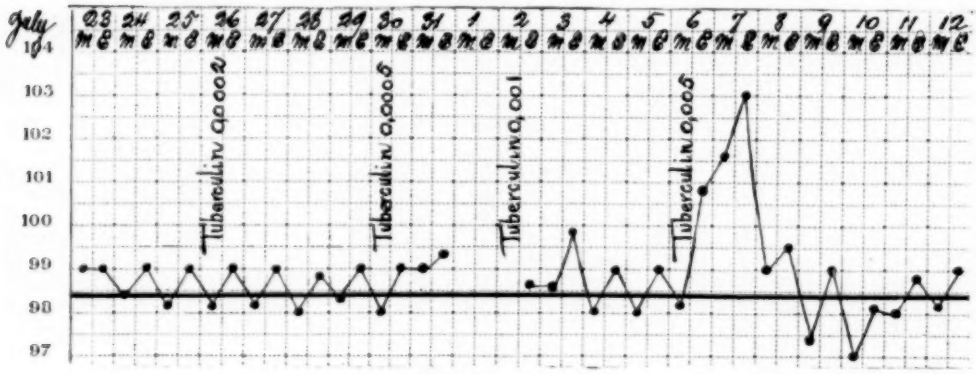

Chart No. 21.

increased roughness or an accentuation of inspiratory sacculations he interprets as ample evidence. We have not felt confidence enough in our ability to predicate unmistakably such slight changes and have made the finding of râles where there were none before or a definite increase in

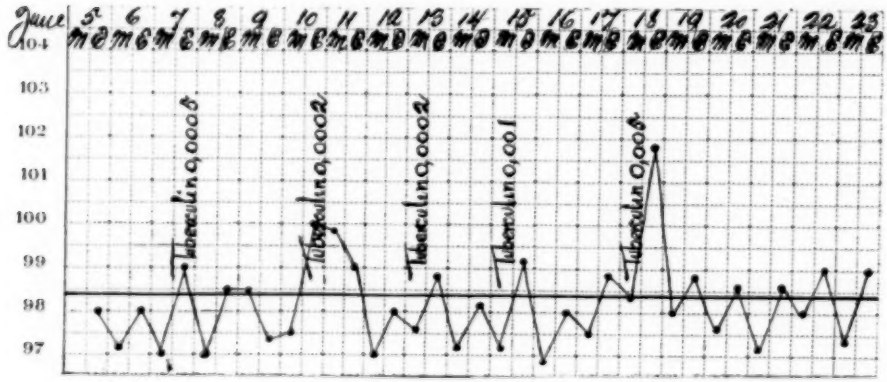

Chart No. 22.

number or extent of pre-existing râles our criterion. In our 63 suspected cases that reacted there was a well-marked change in the local physical signs in 14; in 9 more there were suggestive but not definite changes; in

37 there was absolutely no change; in 3 the history notes are incomplete. In 13 cases with definite pulmonary lesions, 8 gave signs of a focal reaction, 4 showed no change in the physical signs and in 1 the physical signs almost entirely disappeared. This latter observation is unique in our

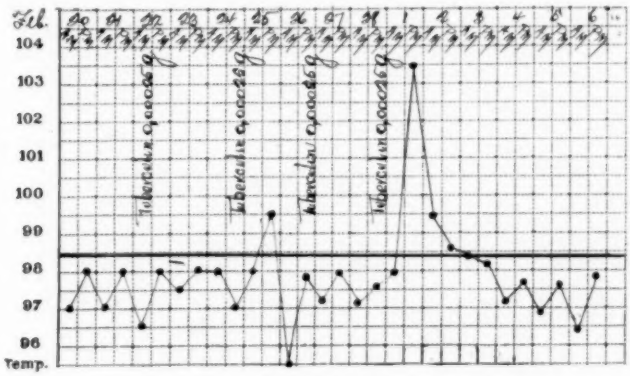

Chart No. 23.

experience. The patient whose case is shown in Chart 23, a girl, aged 17 years, had dulness, suppressed breath sounds and numerous moist and a few sibilant râles over the left back from the angle of the scapula to the base. The lesion having persisted for about six weeks without any change

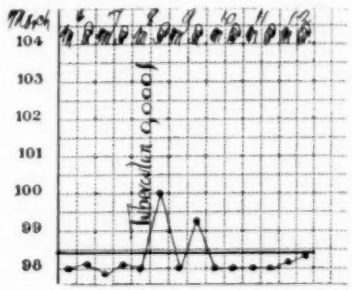

Chart No. 24.

in the physical signs, the patient was given tuberculin. Four doses of ¼ mg. each were administered, and after the second the temperature rose to 99.5, after the fourth to 103.5. There were well-marked constitutional symptoms with cough and expectoration, which had been absent before.

The sputum showed no tubercle bacilli. There was great pain, redness and swelling at the site of injection. After the second dose the râles were fewer in number. After the fourth they had almost completely disappeared. One month later the râles had returned and still persist, almost a year after the reaction. We can not say definitely that the pulmonary lesion in this case is tuberculous; it may have been an unusual coincidence, but a very striking association it is. The absence of the signs of a focal reaction in 46 cases that reacted may be accounted for by supposing that in a certain number the tuberculous lesion was not in the lungs, and in those in which there was a pulmonary focus that the reaction may

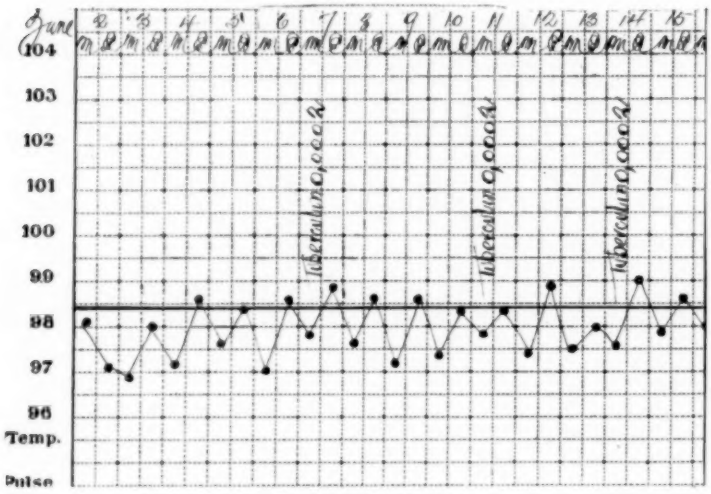

Chart No. 25.

have been too mild to make a difference in the physical signs or the focus too deep to be appreciated by our methods of investigation.

Of 15 suspected cases reacting to doses under 1 mg., 2 gave a focal reaction. Of 45 suspected cases reacting to doses of 1 mg. or over, 12 gave a focal reaction. Of 4 definite cases reacting to doses under 1 mg., 2 gave a focal reaction. Of 8 definite cases reacting to doses of 1 mg. or over, 6 gave a focal reaction. Of the 6 last mentioned, however, 2 showed focal reactions to doses under 1 mg., but no febrile reaction.

Of 6 suspected cases showing a mild reaction, 1 gave signs of a focal reaction. Of 33 suspected cases showing a moderate reaction, 7 gave

signs of a focal reaction. Of 19 suspected cases showing a severe reaction, 6 gave signs of a focal reaction.

These figures show a larger number of focal reactions to high doses and in cases with severe reactions. There is, however, no constant relation between the height and duration of the febrile reaction or the severity of the constitutional symptoms and the focal changes. In Case 42, without a high temperature reaction and with but slight constitutional symptoms, the signs of the focal reaction were particularly striking. In the case shown in Chart 24 they were, too, unusually well marked. In many instances with most severe constitutional symptoms and high fever there was no focal reaction. In the cases shown in Charts 25 and 26,

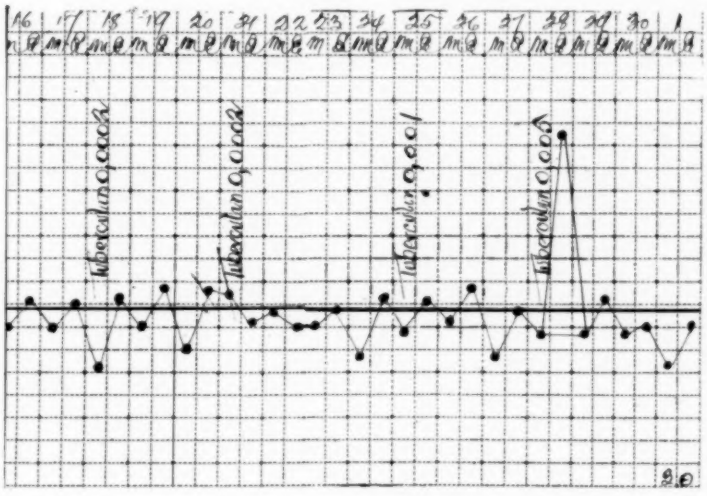

Chart No. 25—Continued.

with definite signs of disease, the focal reaction occurred long before the febrile reaction. In both of these cases the physical signs spread very markedly, and in one case they had not receded after eight months, and in the other they have not completely receded after ten months, although the patient's general condition is greatly improved and all his symptoms have disappeared. The case shown in Chart 27 is of particular interest.

The patient had suggestive symptoms but no definite signs of pulmonary disease. After the second dose of one-fifth of a milligram the temperature rose to 100. After none of the others did it go over 99.2. Following the second injection showers of râles were heard above the

left clavicle and in the left supraspinous fossa. These then disappeared to become evident again after the injection of 10 milligrams. In order to control these observations a second series of injections was given and again after the second and eighth injections the same profuse shower of râles was heard and less numerous râles after some of the intermediate doses. When tuberculin was stopped the râles disappeared.

THE CRITERIA OF A REACTION TO TUBERCULIN.

When the four cardinal symptoms of a tuberculin reaction are present there is no difficulty in making a positive statement; but, as our analysis has shown, such an occurrence is uncommon, and in some instances where only one or even two are present there may be difficulty in definitely deciding that the patient has tuberculin hypersensitiveness. The most important of the four features is without doubt the signs of a focal

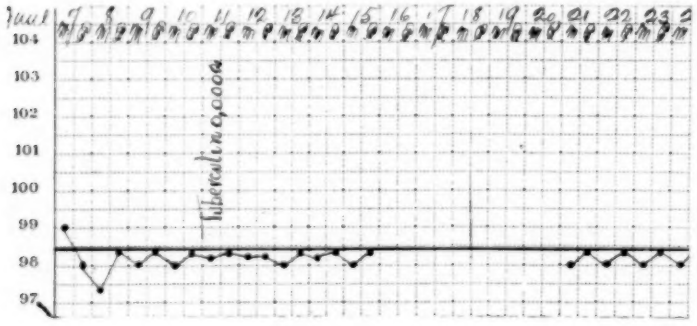

Chart No. 26.

reaction, and in the case shown in Chart 27, to which reference has just been made, I am sure no one would hesitate to call the reaction positive, although there is only one rise of temperature above normal, and this unaccompanied by any marked constitutional symptoms. In the case shown in Chart 28, after several rises to 99, the temperature goes to 99.2 after the seventh injection, and then there is no further rise even after 10 mg. In Chart 29 the temperature goes to 100 after the second dose and then there is no further rise. In Case 84 the temperature rises after 1 mg. to 100.5 and then no reaction to 5 mg. In Chart 19 it goes to 99.4 after the first injection. In none of these were there any constitutional symptoms or signs of a focal reaction, but the case, shown in Chart 19, showed a marked local reaction after the first dose. We have considered all four of these negative, although it must be admitted

that No. 19 possessed a certain grade of tuberculin hypersensitiveness. Möller[25] and Hammer[26] call attention to the frequent occurrence of such slight temperature rises after the first doses of tuberculin and they, too, consider them negative if there is no rise to subsequent higher doses. The case shown in Chart 20 shows no febrile reaction and no constitutional symptoms, but a marked local reaction after the first and second dose. This case, too, we have considered negative although there must have been some hypersensitiveness. The patient whose case is shown in Chart 30 had an old tuberculous knee with cough and indefinite pulmonary signs. She gave the most marked local reactions of any case in our series, each injection being followed by a large tumor with swelling of the adjacent lymph glands. Oddly enough, the injections in the right side of the back were invariably followed by more marked swelling than those in the left. As the chart shows, there was never a marked rise of

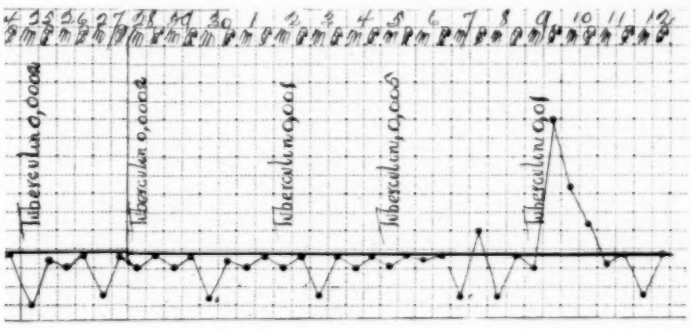

Chart No. 26—Continued.

temperature and there were only very slight constitutional symptoms. It is not easy to decide whether one should call such a reaction positive or negative. It gives some support to the view that local reactions with only slight fever and slight constitutional symptoms indicate healed rather that active lesions. Chart 31, too, presents difficulties in interpretation. Constitutional symptoms were present only after 10 mg. There was a marked local reaction after the fifth and ninth injections. The case shown in Chart 32 illustrates the irregular type of reaction which often occurs in advanced pulmonary tuberculosis. There is more of a general increase in the fever variations associated with signs of a marked focal reaction than an abrupt rise.

25. In Schroeder-Blumenfeld: Therapie d. Lungenschwindsucht, Leipsic, 1904.
26. Beitr. z. Klin. d. Tuberk., 1904, ii, 285.

THE DANGERS OF A TUBERCULIN REACTION.

Möller, Trudeau and other men of large experience assure us that when protected with reasonable caution the test has no dangers. There has, however, grown up in the use of tuberculin therapeutically a strong feeling that reactions are fraught with danger to the patient; and such a careful observer as Sahli refuses ever to produce a reaction purposely even to establish a diagnosis. Certainly in the two cases previously referred to the existing signs rapidly spread while diagnostic doses of tuberculin were being given and did not recede when the reaction subsided. It is true that these were definite cases of pulmonary tuberculosis and tuberculin was not needed to confirm the diagnosis, but they have impressed on us caution, and I feel strongly that tuberculin should be used as an aid in diagnosis only when our usual methods of investigation have failed to give a definite conclusion. This still leaves a field wide enough. One can not look with indifference on a reagent which may produce such

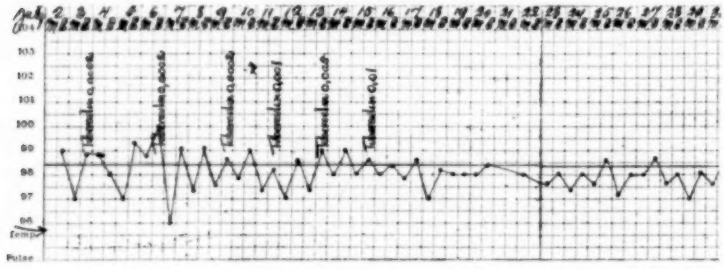

Chart No. 27.

intense constitutional symptoms and such prolonged periods of fever as in the instances we have cited. However, in none of our doubtful cases did any signs or symptoms remain which could be interpreted as permanent injuries from the use of tuberculin.

THE CLINICAL INTERPRETATION OF TUBERCULIN HYPERSENSITIVENESS.

A positive tuberculin reaction means tuberculin hypersensitiveness, and as veterinary practice has shown, tuberculin hypersensitiveness signifies a previous intimate contact with the tubercle bacillus. It is a notorious experience both in veterinary and in medical practice that animals with advanced tuberculous lesions fail to show tuberculin hypersensitiveness, for which we have already given a theoretical explanation; at any rate there is never any question of diagnosis in such instances, and in doubtful cases a negative tuberculin reaction means that the

patient has no active tuberculous lesion. Prolonged clinical observation of such negative cases has invariably lent support to this view, and while it need not theoretically be absolutely certain, practically it nearly approaches certainty. The interpretation of a positive reaction is by no means so simple. The statistics of Naegeli[27] and Burkhardt[28] show how wide the distribution of the tubercle bacillus is among human beings, and it becomes a matter for practical demonstration to show under what conditions these infected individuals show tuberculin hypersensitiveness. One is immediately struck, in looking at any large set of statistics of the tuberculin test, by the fact that so many individuals react. Beck[29] reports observations on 2,508 patients, and of these 1,525, or 60.8 per cent., react; 371 were definitely tuberculous and all reacted; 423 were suspected of having tuberculosis, and of these 364 reacted; 1,714 were convalescents or patients ill with other diseases, and none were suspected of having tuberculous lesions; 790, or 46.1 per cent., reacted.

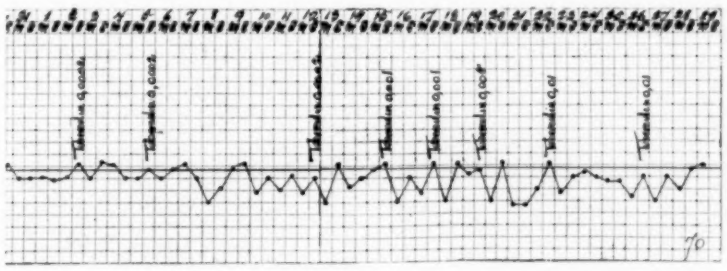

Chart No. 27—Continued.

These figures bear a striking resemblance to Burkhardt's statistics of 1,262 autopsies on adults. Tuberculous lesions were found in practically all and showed signs of activity in 62.5 per cent. Franz[30] injected 400 recruits of the Bohemian Army and 61 per cent. reacted. Fraenkel[16,24] reports 200 observations. Of 56 tuberculous cases all reacted; of 76 suspected cases 70 reacted; of 68 unsuspected patients 37, or 56 per cent., reacted. Of Bandelier's 500 suspected cases all but 37 reacted; of Hammer's 180, 164 reacted. Roth-Schultz reports, of 670 men 98.5 per cent. reactions, of 299 women 96.3 per cent. These patients all had

27. Naegeli cit. Burkhardt: Heft i, p. 139.
28. Ztschr. f. Hyg., liii, Heft i, p. 139.
29. Deutsch. med. Wchnschr., 1899, Nos. 5-9.
30. München med. Wchnschr., 1902, No. 7, p. 302.

symptoms or physical signs suggesting a pulmonary lesion. Of our 94 cases 11 were definitely tuberculous and all reacted, 75 were suspected cases and 63 reacted, 8 were patients with disease other than tuberculosis and 4 reacted. From these figures it is apparent, then, that about 90 per cent. of all suspected patients react and about 50 per cent. of patients with diseases other than tuberculosis, or individuals in whom no tuberculous lesion is expected. The objections that have been urged against the universal application of the anatomical records of Naegeli and Burkhardt may be applied with equal force here. The observations have been made for the greater part on general hospital patients, and perhaps the higher strata of society would give a lower percentage. This even seems probable, but we have no figures from which to judge, and it is scarcely to be

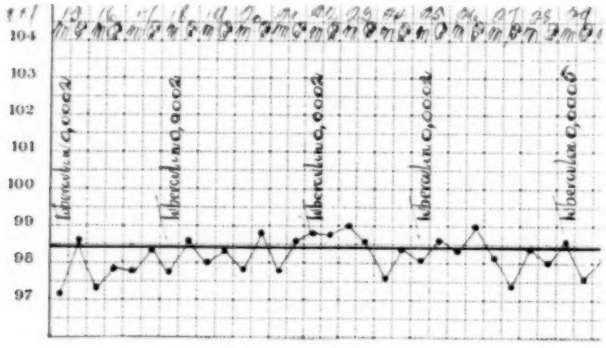

Chart No. 28.

presumed that they would be more than halved. This would still leave 25 per cent. of individuals without any clinical evidence of a tuberculous lesion presenting tuberculin hypersensitiveness.

There has grown up a widespread feeling of mistrust, or at least of suspicion, of sanitarium statistics. With the demand for the earliest possible cases of tuberculosis some have intimated that the evidence of diagnosis has been too lightly considered and many patients accepted in whom the presence of disease was, to say the least, doubtful. No one has been more conscious of such criticism than sanitarium physicians themselves, and they have made every effort to fortify their position. To get results in any way commensurate with the great expense of equipment and maintenance only early cases can be treated. No one would think of demanding the presence of tubercle bacilli in the sputum as the criterion for admission. Still we all know that the early symptoms of pul-

monary tuberculosis are often vague, the signs inconclusive and our judgment frequently faulty. Less than 50 per cent.[31] of the patients admitted to the German sanatoria have tubercle bacilli in their sputum. In the majority the diagnosis depends upon the skill and judgment of the physician in charge. Men of experience these are, and far from criticising their methods I most heartily support them. I believe firmly that the tendency is the correct one, and to achieve the best results let us treat a few cases that do not absolutely demand it, confident of the honesty of our aim and the general success of our method. Unfortunately the error in diagnosis is many hundred times on the side of conservatism to once on the side of radicalism. It must, however, be granted that in exceptional cases one man might offer a positive opinion where another

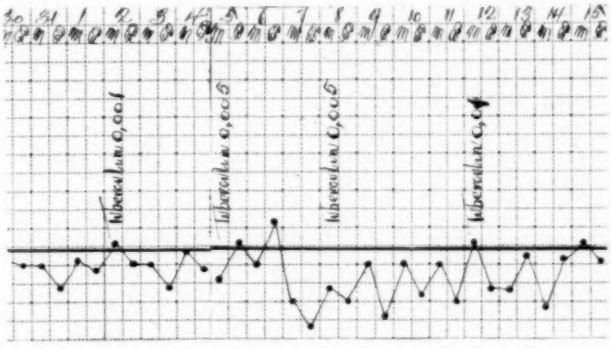

Chart No. 28—Continued.

would express doubt and a third deny—and all three might be men of ability and experience. In a well-conducted sanatorium a certain number of such—let us call them questionable—cases must be admitted, and if tuberculin is to render us a service in diagnosis here is its especial field.

Now in justification of sanatorium records Bandelier quotes his results. Of 500 cases admitted to the sanatorium with symptoms or signs pointing to an early pulmonary tuberculous lesion, but without tubercle bacilli in their sputum, all but 37 reacted. This small percentage of error demonstrates glowingly, he thinks, that sanitaria treat and cure tuberculous patients. These 37 negative cases, however, had no clinical features by which they could have been distinguished from the 463 that reacted and would have been kept in the sanatorium and treated had

31. Pickert: Ztschr. f. Tuberku., 1903, iv, 21.

tuberculin not been used. Certainly in our own cases a number of the patients that failed to react had far more definite symptoms and signs of tuberculosis than many that did react. If tuberculin did no more then differentiate 7.4 per cent. of Bandelier's cases, 9 per cent. of Hammer's and 16 per cent. of our own and stamp these definitely as not tuberculous it would still be well worth its use. What we take exception to is the attitude that a positive tuberculin reaction marks a patient not only as a suitable candidate for sanatorium treatment, but one urgently in need of it. In the view of our own experience and of the figures we have quoted we can not believe that tuberculin gives "absolute certainty" to a diagnosis or that it alone can place sanatorium statistics on an "irreproachable basis" (Bandelier). In speaking of a diagnosis we refer, of course, to a diagnosis of pulmonary tuberculosis, and let us add the qualifying adjective, *clinical* tuberculosis. As an example, a man comes complaining of pulmonary symptoms and the examination shows indefinite signs at one apex. He is given tuberculin. If he fails to react, our suspicion is dispersed. If he reacts we know that over 25 per cent. of patients without a suspicion of tuberculosis react, and in weighing the evidence I contend that we reach our conclusions more from a consideration of the symptoms and physical signs than from the tuberculin reaction. It adds a new bit of evidence to what we already have, and even an important bit of evidence, but it does not decide the diagnosis absolutely and indisputably mark the patient as a candidate for sanatorium treatment. It is of value only when viewed as a part of the general clinical picture and can not be compared in significance to finding tubercle bacilli in the sputum nor yet to such a characteristic symptom as a frank hemoptysis. It should be remembered, too, that when a patient reacts to tuberculin this is no assurance that the disease from which he is suffering is tuberculosis. Of our eight cases with diseases other than tuberculosis four reacted; one had arthritis deformans, one neurasthenia with abdominal symptoms and one bronchiectasis. The fourth case had a swelling of the wrist joint the diagnosis of which lay between tuberculosis and sarcoma. The patient gave a typical reaction to the first injection of 1/5 mg. of tuberculin. At operation the swelling proved to be sarcoma.

What we have said about the tuberculin reaction in relation to diagnosis has reference only to those cases in which no signs of a focal reaction are discovered. When a patient reacts to tuberculin and during the reaction a perfectly definite change is made out in the physical signs, the method becomes one of the most satisfactory diagnostic aids we possess.

We then know that the patient has tuberculosis, where he has it and something about its extent.

In our 75 suspected cases, then, we obtained positive information in 26, 12 being negative and 14 showing signs of a focal reaction. Surely these results alone would justify the use of the method. In the remaining 37 cases that reacted we formed our opinion only after full consideration of all the features. A number of them we felt sure were not pulmonary tuberculosis, and their future course has justified our opinion.

THE CLINICAL METHOD OF DEMONSTRATING TUBERCULIN HYPERSENSITIVENESS.

Koch's original method of giving tuberculin was to inject 1 mg., 5 mg. and then 10 mg., and if there was no reaction to repeat the last dose.

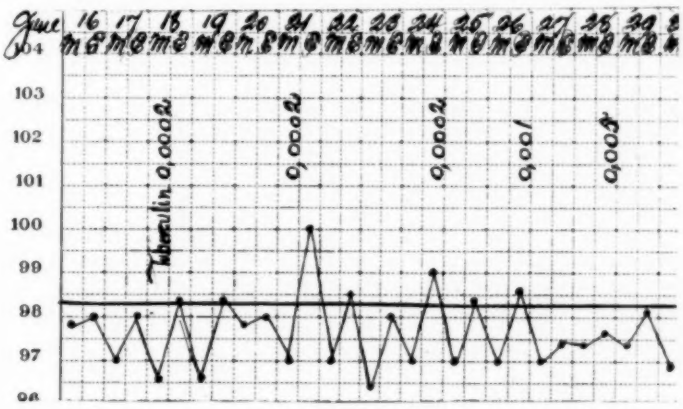

Chart No. 29.

Bandelier has advocated that this plan be strictly adhered to. Löwenstein developed the method of repeating small doses and has proposed the repetition of 1/5 mg. four times. As Raepke very justly objects, too many cases of early and definite pulmonary tuberculosis fail to react to this procedure to make it of satisfactory general application. In 28 of our cases that reacted small doses (less than one-half milligram) were repeated at least three times before ascending to larger; 15 reacted to such repetition, while 13 required higher doses; 5 of the 15 reacted to the first dose, 3 to the second, 2 to the third, 4 to the fourth and 1 to the fifth. Of the 13 requiring higher doses 8 had a small dose repeated three times, 3 four times, 1 five times and 1 eight times; 4 of the cases

that failed to react to the repeated small doses were definitely pulmonary tuberculosis. Repeated injections of tuberculin not only produce hypersusceptibility but they may under certain conditions bring about an obliteration of pre-existing hypersensitiveness. Just what these conditions are we do not know. I quite agree with Köhler, who emphasizes that we can never predict just what will follow an injection of tuberculin. We have no means of judging whether a patient will react to a small dose or to a large dose, mildly or severely. What we aim at is to begin a little below the minimal reacting dose and ascend gradually. No definite routine can be laid down to fit every case. We modify our method to suit conditions as they arise. I do not think there are ten cases in the whole series who have received injections just alike. At present our scheme

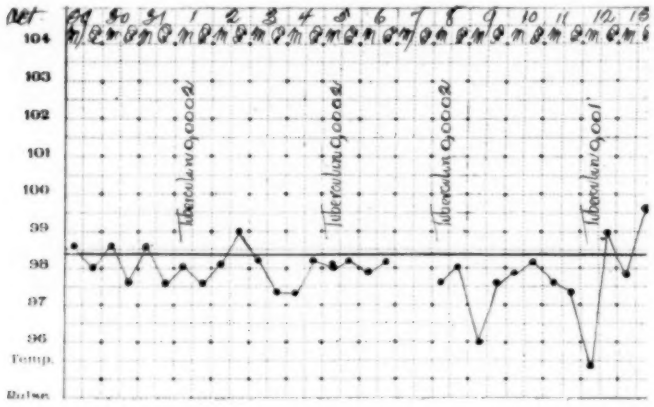

Chart No. 30.

is to give 1/5 mg., 1/2 mg., 1 mg. and 5 mg., but we seldom carry it out in such regular progression. Whenever a patient shows a tendency to react to a given dose, instead of following it with a larger the same dose should be repeated. In the cases shown in Charts Nos. 21, 33 and 34 the severe reaction might have been avoided had this rule been followed. It is, however, not of universal application, as Charts Nos. 35, 36, 37 and 22 illustrate. We begin with 1/5 mg. because we have found that it is exceptional for a patient to react to this initial dose. Of course occasionally patients will react even to much smaller doses, and Chart No. 38 shows a typical reaction to 1/1,000 mg. In children the initial dose should never be over 1/10 mg. and it is often best to begin with 1/20 mg. The terminal dose, too, should seldom be over 1 mg. This

question of the optional terminal dose has evoked much discussion. Koch makes 10 mg. the border beyond which even normal individuals may react; however, it would seem quite arbitrarily. Goetsch[32] insists that we must give 50 mg. to definitely exclude tuberculosis. We know that for healthy guinea-pigs there is no maximal dose, for they may stand as much as 20 c.c. without dying. There is no evidence to show that normal human beings are any more susceptible than guinea-pigs, but it is evident that there would be difficulty in establishing the point. It must be remembered that in using tuberculin we do not wish to discover trifling evidences of susceptibility, and as the results of the test are at best inconclusive it would seem that a restriction to moderately small doses would after all serve our purpose best. Raepke in a large number of cases got

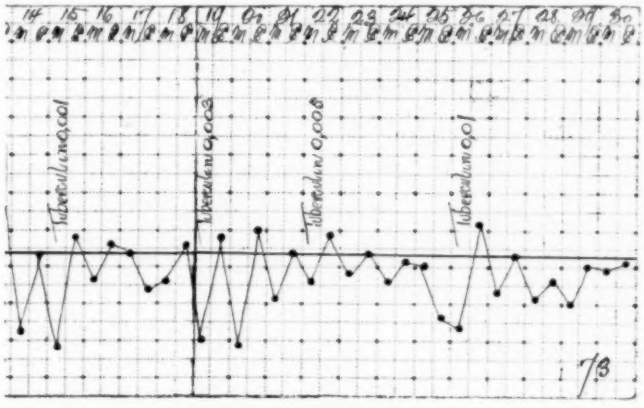

Chart No. 30—Continued.

as large a proportion of reactions with 5 mg. as he did with 10 mg. as the maximal doses. Turban,[33] Beck and Möller have shown that it is especially the early, fresh lesions which produce the most marked hypersensitiveness, and it is these cases particularly that we seek to recognize.

THE CUTANEOUS AND THE CONJUNCTIVAL TESTS.

During the past year two valuable contributions have been made to the use of tuberculin in diagnosis. Both of these methods depend upon the utilization of the local reaction as an index of tuberculin hypersen-

32. Goetsch. cit. Bandelier; see Note 5.

33. Turban: Beitrage zur Kentniss der Lungentuberkulose, Wiesbaden, 1899.

sitiveness without the production of fever, constitutional symptoms or a focal reaction. Von Pirquet[34] announced in May, 1907, that by putting a drop of tuberculin on the skin and making an abrasion through it most remarkable variations might be observed in the manner in which different individuals reacted. In the tuberculous patient the area becomes red in eight to twelve hours, then swollen and infiltrated, and in severe reactions vesiculation may occur. Occasionally the reaction may be delayed for thirty-six or forty-eight hours, when it is usually very mild; or it may develop a few hours after inoculation and rapidly subside. In a discussion of Von Pirquet's report, Wolff-Eisner stated that a similar reaction could be obtained by instilling a drop of tuberculin into the conjunctiva. Apparently quite independently Calmette made a similar observation and reported his method in June, 1907. The literature on

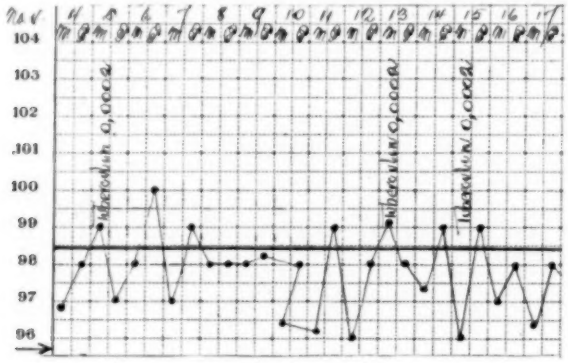

Chart No. 31.

these two reactions is already voluminous, but Wolff-Eisner[35] has collected it and given an exhaustive review of the results. During the past six months we have been using both methods for diagnosis, and although we are not prepared to give a detailed account of our experience I shall briefly refer to it. It is now generally conceded that, although the skin reaction is specific, it is too delicate a reaction to be of much service in diagnosis. Von Pirquet himself noted that nearly all adults reacted, and restricted the value of the method to early infancy. It is most interesting to see in his tables how the percentage of reactions steadily increases with advancing years: 0 to 4 months, 0 per cent.; 4 to 12

34. Berl. klin. Wchnschr., 1907, Nos. 22-23.
35. Beitr. z. Klin. d. Tuberk., 1908, ix, No. 1.

months, 10 per cent.; 1 to 3 years, 24 per cent.; 3 to 5 years, 37 per cent.; 5 to 8 years, 56 per cent.; 8 to 14 years, 60 per cent. Almost as many apparently healthy adults react as suspected cases. Of 360 tuberculous children, 88 per cent. reacted, the negative cases all being far advanced. In 100 autopsies on children from 1 to 14 years of age, 30 cases that had reacted all showed tuberculous lesions and 17 more had advanced or miliary tuberculosis that did not react. The other 54 cases were apparently free from tuberculosis and only one had reacted. In our earlier observations we placed a small drop of pure tuberculin on the skin of the arm and made a superficial abrasion through it. Secondary abrasions were made as controls on the bare skin or through a drop of 50 per cent. glycerin. We have never observed a reaction in any of the controls. Recently we have aimed to refine the methods by testing various dilutions

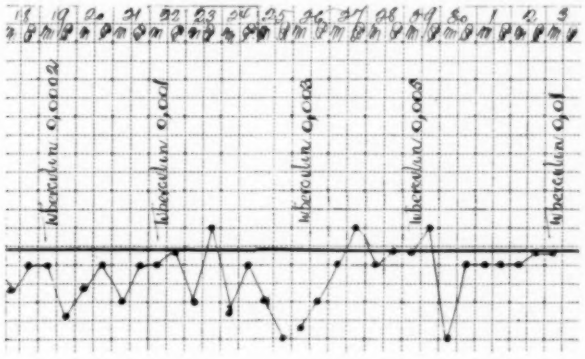

Chart No. 31—Continued.

from 1 to 20 per cent. In 137 observations by the older methods 60 cases were definitely tuberculous, 49 reacted, 11 did not. Of the 11 negative cases 9 were being treated with tuberculin and 2 were advanced cases. In 46 cases suspected of having tuberculosis, 26 reacted, 20 did not. In 11 cases of illness other than tuberculosis, 6 reacted, 5 did not; 2 had valvular heart disease, 1 lobar pneumonia, 2 neurasthenia, 1 ozena, 4 typhoid fever. Of 19 apparently healthy individuals, 14 reacted, 5 did not. These figures correspond closely with the average reports and illustrate that too many latent or insignificant lesions react for the method to be of much value in diagnosis unless the result be negative.

In performing the eye test Wolff-Eisner and most German observers use dilutions of old tuberculin varying in strength from 1 to 5 per cent.

To get rid of the glycerin and culture products Calmette precipitates old tuberculin with alcohol and dissolves the sediment in normal salt solution in strengths of from ½ to 2 per cent. Our own observations have shown us conclusively that glycerin in 1 per cent. solution will not cause any conjunctival irritation, and we see no reason why simple dilutions of tuberculin should not give results as satisfactory as the purified product. In our early observations we used a 1 per cent. and 2 per cent. solution of purified tuberculin furnished us by Dr. Baldwin of Saranac Lake; more recently, simple dilutions of old tuberculin. Our present routine is to instil a drop of measured volume of a 1 per cent. solution into one eye, if there is no reaction a drop of a 2 per cent. solution into the other, and if still no reaction after an interval of three to four days, another drop of a 1 per cent. solution into the first eye. Baldwin[36] and Smithies

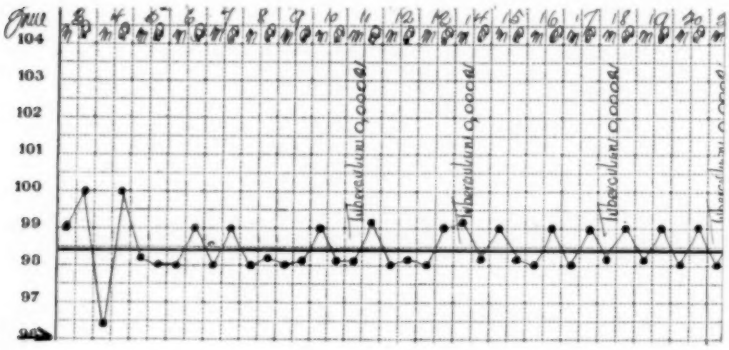

Chart No. 32.

and Walker[37] give elaborate details of the technic to be employed. We have observations on 104 cases in which the eye test was performed; 90 of these cases were also vaccinated, so the two methods may be compared.

Thirteen cases were diagnosed not tuberculosis. On the first instillation 11 were negative and 2 showed very slight reaction.

On second instillation one case which was slight, became positive and one which was negative became positive.

Five of the cases received a third instillation, 2 remained negative; 2 which had been negative became positive and 1 which was slight was again only slight.

Twelve of these 13 cases were vaccinated. In 4 the reaction was marked; in 6 slight and in 2 negative.

36. Jour. Am. Med. Assn., 1907, xlix, 1969.
37. Jour. Am. Med. Assn., 1908, l, 259.

Of the 4 cases with marked reaction, 1 reacted to eye slightly, one positively to third instillation, 1 on the second and 1 on the first.

Of the 6 cases with a slight reaction, 2 were negative to a single instillation, 1 negative to two instillations and 2 negative to three. One was positive on the second instillation.

Of the two cases with a negative reaction, 1 reacted positively to the second eye test, 1 was negative.

Twenty-four cases were definitely tuberculous.

First stage, 8 cases: Two positive to first eye test and 1 slight; 2 positive to second instillation; 2 negative to a single instillation and 1 negative to two. Two of the negative cases had tubercle bacilli in their sputum. All of the 8 cases were vaccinated. Six gave a marked reaction; 4 of these reacted to the eye test, 1 was slight and 1 negative. One gave a slight reaction; the eye was negative. One case was negative to vaccination and the eye test but had tubercle bacilli in the sputum.

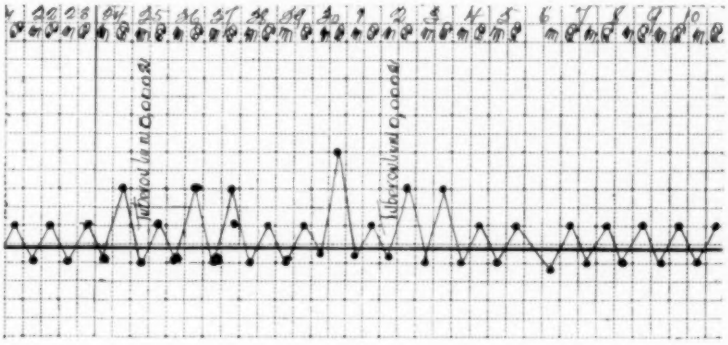

Chart No. 32—Continued.

Second stage, 5 cases: Three positive to first eye test and 1 negative; 1 was negative to 3 instillations. Vaccination: Four gave marked reaction; 1 was negative to vaccination and to all three eye tests.

Third stage, 9 cases: Two positive to first instillation and 1 slight; 1 positive to second instillation; five were negative, 3 to one instillation, 1 to two, and 1 to three. Eight of these cases were vaccinated. Five gave a marked reaction; 3 gave positive eye test; 1 slight and 1 negative. One gave a slight reaction; eye test slight. Two were negative to vaccination and to eye test.

An old, apparently healed pulmonary lesion showed no eye reaction to two instillations.

One patient with an old tuberculous knee and symptoms of an early pulmonary lesion gave a marked reaction to vaccination and to the first eye test.

Fifty-six cases were suspected of having pulmonary tuberculosis. Eleven gave a definite eye reaction, 4 to the first instillation, 2 to the second, and 5 to the third. Twelve gave a slight eye reaction, 4 to the first, 7 to the second, and

1 to the third. Thirty-three were negative, 17 to one instillation, 5 to two, and 11 to three. Of the 56 cases 54 were vaccinated. Twenty-four gave a marked reaction; 13 gave a mild reaction, and 17 were negative.

These figures show at a glance how much less frequent the eye reaction is than the skin.

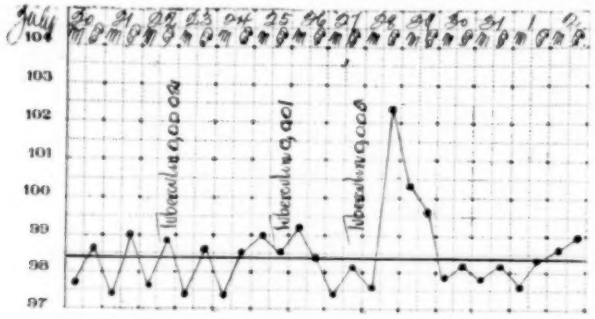

Chart No. 33.

Of 13 non-tuberculous cases, 2 gave a positive eye reaction, 10 a positive skin reaction.

Of 24 definitely tuberculous cases, 10 gave a definite eye reaction, 17 gave a definite skin reaction.

Of 56 suspected cases, 6 gave a definite eye reaction, 37 gave a definite skin reaction.

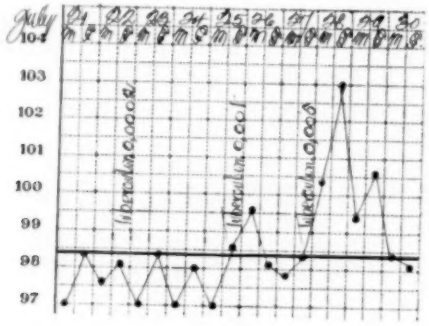

Chart No. 34.

In this summary it will be noticed that I have counted as positive neither the slight eye reactions nor those which became positive only after a third instillation. A slight reaction we have called one in which it was just possible to tell in which eye the drop had been put. The

reaction usually consisted in a little reddening or slight injection of the caruncle. Just what the significance of these extremely mild reactions is we are not yet in a position to say, and at least temporarily we are unwilling to class them as definitely positive reactions. As will be noted

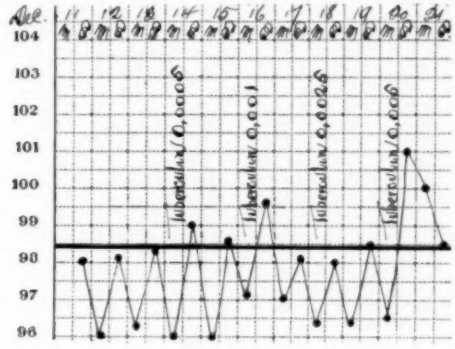

Chart No. 35.

from our figures, 17 suspected cases failed to react to an instillation in each eye, but 5 of these did react when a third dose was given. Now, this third dose was in nearly all instances only half as large as the second

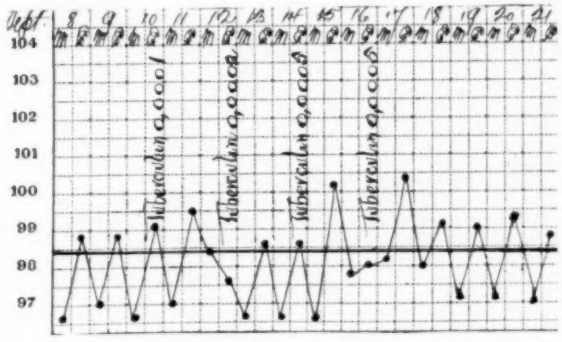

Chart No. 36

dose, and the eye which at first gave no reaction showed most marked inflammatory changes after the second application. Evidently an application of tuberculin causes very remarkable changes in the local susceptibility to its influence. The effects are very similar to the general hyper-

susceptibility developed after the injection of small doses of tuberculin and the mechanism of the development of the two processes is in all probability the same. This reaction upon the instillation of a second dose into the same eye is such a frequent phenomenon that this feature alone

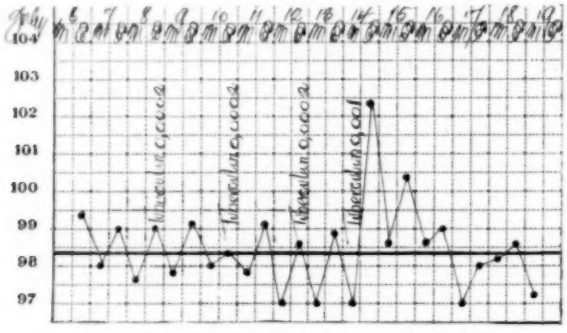

Chart No. 37.

would seem to contradict any relation to the opsonic index of the blood serum. Smithies and Walker consider these second reactions entirely accidental, depending on whether we instil at the crest of an opsonic wave

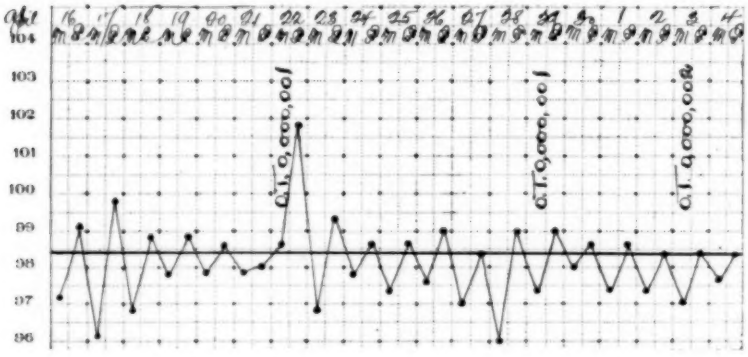

Chart No. 38.

or at the trough. Just what the clinical import of these second reactions is we as yet can not say. The general impression is that they should not be counted as diagnostic reactions. An interesting phenomenon of all local reactions is their tendency to flare up upon subsequent injections of

tuberculin. The case shown in Chart 39 gave an eye and skin reaction and was then put on diagnostic doses of tuberculin. When he reacted to 2 mg. the eye flared up, the points of vaccination become red and prominent, and each area of previous injection a little swollen.

We have then in the eye test a method of applying tuberculin which has at least a marked numerical advantage over the other methods. As our figures show, not nearly so many suspected cases react as to the injection method, but many tuberculous patients do not react and some apparently healthy individuals do. I may say that many observers present figures that are far more convincing than ours and run almost parallel with the clinical diagnosis. However, Wolff-Eisner, the introducer of the

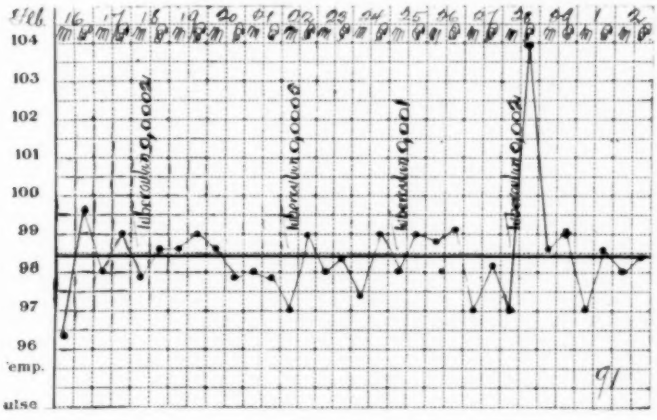

Chart No. 39.

method, reports results closely similar to our own. Only prolonged observation of tested cases will establish satisfactorily the value of the method.

SUMMARY.

To summarize these considerations we would say then that while tuberculin is a valuable aid in the diagnosis of pulmonary tuberculosis it must be used with care and the results interpreted with caution. We believe that the reaction is a specific one, but it must be borne in mind that a very insignificant lesion may produce tuberculin hypersensitiveness and the prevalence of such lesions should be fully realized. A negative reaction we consider decisive information, as is also a focal reaction. In the absence of a focal reaction tuberculin hypersensitiveness

must be viewed as one phase of the clinical picture and our judgment not be too much warped by its presence. As a clinical procedure no routine schema can be advised, as we must alter our method to meet conditions as they arise. For adults some such scale as 1/5, 1/2, 1 and 5 mg. may be suggested; for young children 1/10, 1/5, 1/2 and 1 mg. The cutaneous reaction is too delicate an indicator to be of any value in diagnosis unless the reaction be negative, which it seldom is in adults. The eye reaction gives results more nearly in accord with clinical experience, but by no means absolute certainty. We do not feel that it can supplant the subcutaneous method. It will be well for some time to use the two together, but not simultaneously. The eye inoculations should precede the subcutaneous by at least a few days.

AN EXPERIMENTAL AND CRITICAL STUDY OF THE ETIOLOGY OF CHRONIC NEPHRITIS.*

HAVEN EMERSON, M.D.

NEW YORK.

"It is only when the full etiology of disease is known that the medicine of our day can become the medicine of the future—that is to say, hygiene in its widest sense."—PAWLOW.

CONTENTS.

Introduction—Methods—Selection of material—The effect of alcohol, ether, chloroform and amyl nitrite inhalations—The effect of injury of the kidney by the hypodermic needle, and of normal saline solution, adrenalin and alcohol solutions injected directly into the renal parenchyma—The effect of adrenalin and gelatin solutions injected directly into the veins—Summary of experimental results—Discussion on the etiology of chronic nephritis—Conclusions—Bibliography.

INTRODUCTION.

With the knowledge that the combined death rates from heart and kidney diseases have almost doubled within the past twenty-five years in the cities of Boston, New York and Chicago,[1] there has been offered no sufficient explanation for the cause of this increase, or of the widespread occurrence of nephritis, and no means of prevention are proposed offering any hope that the increase will be checked in the future. Without knowledge of the cause of disease, little of permanent value has ever been done toward its prevention, if one might except the discovery of vaccination for the prevention of smallpox.

While a variety of substances have been used successfully to cause diseased conditions in the kidneys of animals, such as mineral or vegetable poisons or irritants, the toxins of pathogenic bacteria, and nephrotoxins, at present the lesions reported and the conditions created can not be claimed to resemble essentially the lesions of chronic productive nephritis in man, which are found so frequently at autopsy that a normal kidney is a rare exception in an adult.

Recognizing that the accepted etiologic factors mentioned and copied from author to author, from the time of Richard Bright, account for many of the frankly-marked cases which can be followed in an almost unbroken chain of clinical and pathologic evidence from the inception

* Work done under the auspices of and aided by a grant from the Rockefeller Institute for Medical Research in the laboratories of physiology and pathology in the College of Physicians and Surgeons, Columbia University, New York.

1. Darlington: New York Med. Jour., 1907, lxxxv, 1158.

of the disease until death, there remain unexplained the causes of cases of so-called initial nephritis. Chronic inflammatory processes in the kidney are so commonly found at autopsy when there has been no reason to suspect nephritis before death,[2] that we must add many cases of unrecognized nephritis to those which are recognized but which lack sufficient etiologic explanation.

While a variety of causes are known to be responsible for, or to contribute to, the occurrence of chronic interstitial or productive inflammation in various tissues, circulatory disturbance resulting in a stagnation of venous blood or a diminution in the supply of arterial blood, or both, is an almost constant accompaniment, and may in some instances be shown to be the sole cause of the accumulation of connective tissue to the permanent and increasing detriment of the functional activity of the tissue or the organ involved.

The means at our disposal to effect changes in the blood supply of the kidney are few and offer many obstacles in the way of drawing accurate conclusions. The facts given here are based on experimental conditions produced in fourteen dogs over a period of twenty-six months, the plan of tests and observations being outlined in the preceding summary.

METHODS.

Small and medium-sized dogs were used for the experiments. It was found necessary to test the urine of dogs selected, over a period of three months, to eliminate those in which occasional or persistent albuminuria indicated a probable spontaneous or rather existing nephritis of unknown origin.[3] During this period of probation the dogs were kept in large cages, where they had full freedom of movement, and from which they were released at least every second day to run about for a short time, either in the building or in the yard outside. Their diet during this period was water and Spratt's dog biscuit. In selecting the fourteen dogs that were finally used, eleven were rejected because of albuminuria. The prevalence of albuminuria in dogs used for experimental purposes and the need of care in selecting material has been noted by Pearce[3] but so far as I can find there is no mention of such precautions being taken by any other experimenters with dogs or other animals. Inasmuch as removal of a piece of the kidney for diagnostic purposes, before the tests are begun, does not give reliable information as to an existing nephritis, and, moreover, as such a procedure, as will be shown later, tends to the production of such lesions as are being sought for by other

2. Emerson, C. P.: Jour. Am. Med. Assn., 1906, xlvi, 5, 89.

3. Pearce: Univ. Penn. Med. Bull., 1903-4, xvi, 217.

means, we must rely on the urinary examinations as the best, though certainly not a perfect, test for the presence of a nephritis. As Pearce[3] has shown, and as will be shown in the following tests, nephritis may exist in dogs without albumin or casts being constantly or at any time present in the urine.

The dogs that were finally selected were kept continuously on the diet described above, with occasional changes to meat diet, for periods of a week or two every six months. All but three of the dogs suffered from mange at one time or another while they were under observation, and most of them recovered completely from it by the application of 10 per cent. sulphur ointment to the skin. Several of the dogs had attacks of diarrhea, which were checked by a dose of castor oil and a diet of milk.

Three classes of test procedures were used: (A) inhalations, (B) hypodermic injections into the kidney substance, and (C) hypodermic injections into the veins or the muscles of the legs.

(A) INHALATION METHOD.

Alcohol, ether, chloroform and amyl nitrite were used to see if the repeated use of general vasodilators would produce any appreciable changes in the functions or structure of the kidney. The dog was placed in an air-tight wooden box, provided with two glass windows in the top, and an entrance tube for air at one end connecting directly with the supply flask, and an exit tube for air at the other end, provided with a mica valve so adjusted as to prevent the entrance of air, but allowing air to pass out when the pressure in the box was only slightly over atmospheric pressure.

The supply flask was connected by a one-half inch rubber tube with the entrance tube of the box by one opening, and to the tube of an artificial respiration apparatus by the other opening. A third and very small tube, with a stop-cock, in the cork of the supply flask allowed of the administration of the desired amount of the drug to be used. The flask was immersed in a pail of water, which was kept at a temperature of from 30° to 35° C. during alcohol administration, and at from 17° to 20° C. when ether, chloroform and amyl nitrite were being given.

Air was supplied by an artificial respiration apparatus at the rate of 35.5 respirations a minute, and each inspiratory blast had a volume of 400 c.c. Thus the dogs were supplied with 14,200 c.c. of air a minute. As the air passed into the supply flask and out of it into the box it carried with it some of the vapor of the drug to be administered. Knowing the time taken in evaporating the volume of the drug put into the supply bottle, and the amount of the drug and of the air supply being known.

it was found that the percentage of the drug present in the air which the dog breathed was as follows:

For alcohol during 30 minutes	.01765	per cent.
For ether during 30 minutes	.03521	per cent.
For chloroform during 30 minutes	.007	per cent.
For amyl nitrite during 15 minutes	.0018	per cent.

There was little or no struggling of the animals in the box, as the administration of the drugs was gradual, and after a few treatments the dogs usually kept perfectly quiet and relaxed on the floor of the box.

The respirations and the color of the nose and lips could be watched through the windows in the box, and indications of failing circulation were met by opening the box or by connecting the air supply tube directly with the entrance tube of the box, cutting out the supply flask from the circuit. Squibb's ether, and chloroform, and amyl nitrite were used, and absolute alcohol was used. After the treatment was finished the dog was allowed to recover gradually from the effect of the drug, and when muscular co-ordination was restored he was taken to the cage again.

(B) HYPODERMIC INJECTIONS INTO THE KIDNEY SUBSTANCE.

The skin was shaved over the lumbar region on the left side and then washed over with 95 per cent. alcohol. The kidney was then fixed as well as possible with one hand, and a long hypodermic needle was passed through the skin and lumbar muscle until the kidney was felt. The needle point was then passed through the capsule and the dose of the drug injected. This procedure was not always successful, but tests on the cadaver, and on many dogs which were used for other purposes, and observed with the kidney and needle *in situ*, make me feel confident that the majority of attempts were successful.

To control these tests two dogs were used in which no drug was given. In one the needle was simply inserted into the renal parenchyma and withdrawn, and in the other 6 c.c. of normal saline solution were injected into the kidney substance. The alcohol and adrenalin chlorid solutions were used to test the possibility of affecting the blood supply of the kidney locally without injuring the parenchyma primarily. The alcohol was used in 25 per cent. strength in normal salt solution, and the adrenalin chlorid was used in 1 to 1,000 solution.

(C) INTRAVENOUS INJECTIONS.

The veins of the leg were used and aseptic precautions were observed. A 10 per cent. aqueous solution of acetate of lead was used to obtain a standard type of chronic toxic nephritis. A 1 to 1,000 solution of

adrenalin chlorid was used to see if general vasoconstriction would produce any secondary results in the kidney. A 5 per cent. solution of gelatin in water, which was fluid at body temperature, was used to test the effect of persistently increased viscosity of the blood upon renal function and structure, the gelatin being injected through a warmed syringe with a small aspirating needle.

URINARY TESTS.

The urine was collected at intervals during the course of treatment, the dog being kept in a metabolism cage for a day or two for the sake of obtaining a clean sample of urine. The urine was tested as to its specific gravity, for albumin by the use of heat and nitric acid, and microscopically for casts. It may be properly noted here that casts were not found in any case.

HISTOLOGIC MATERIAL.

At the autopsy specimens of the various organs were hardened in equal parts of Mueller's solution and 5 per cent. formalin and were later washed, imbedded in celloidin, sectioned, stained in hematoxylin and eosin, and mounted in balsam.

A. EFFECTS ON THE KIDNEY OF REPEATED GENERAL VASOMOTOR DILATATION.

ALCOHOL.

In spite of the disagreement among physiologists and among clinicians as to the position alcohol holds in nutrition, there is substantial agreement as to its effect on the circulation. The best summary of results is found in the recent observations of W. E. Dixon,[4] who reaches the following conclusions.

"Alcohol does not affect all the vessels in the intact animal in the same way.

"Alcohol dilates the vessels of the skin rapidly, and tends to constrict the vessels in muscle tissue, and to a less marked degree in the splanchnic area, large doses causing immediate splanchnic constriction.

"The usual effect in man is a central one, causing superficial dilatation and internal constriction. This is the reaction of the organism against the rise of temperature which the increased metabolism would otherwise result in. Central stimulation (or stimulation of the corpus striatum) causes increased metabolism.

"The sum total of general pressure changes due to alcohol is usually a vasodilatation."

4. Dixon: Jour. Physiol., 1907, xxxv, 346.

We may suppose, therefore, that the frequent administration of alcohol to an animal would subject the kidney to fluctuations in its vascular supply. Periods when there was a decided decrease in the blood bulk passing through the kidney, owing to a lowered general pressure and construction of the splanchnic vessels, would result.

PROTOCOL 1.

Dog.—White male fox terrier; weight, 8290 G. Urine, free from albumin and casts; specific gravity, 1013. Diet, dog biscuit and water. Probation period, July 1 to Sept. 15, 1905. Normal respiration and pulse at rest, 20 and 100.

Alcohol was administered by the inhalation method at intervals of a few days from Sept. 5, 1905, to March 17, 1906, the doses varying from 25 c.c. to 60 c.c., and the total amount of absolute alcohol used being 700 c.c. The duration of muscular incoordination averaged two hours at each administration. A marked and unexpected result of this method of administering alcohol was the extreme rapidity of respiration and the change in the pulse-respiration ratio. At the height of the effect, usually at the end of fifteen minutes, the respirations increased to from 220 to 260 a minute, and when on several occasions the dog was removed from the box for better observation of this phenomenon, the pulse was found to be from 120 to 130 a minute, the respirations remaining at 220 or more. This was in no way to be mistaken for dyspnea, as the tongue and nose were pink and the rapid respirations persisted for some minutes after the dog was removed from the inhalation box. Furthermore, neither this dog, nor the others tested in the box, showed any evidence of dyspnea when supplied with air alone, and in all probability this was a manifestation of excessive central irritation.

March 17, 1906: Weight, 9,300 G.; appears in good condition, has had no mange; urine contains marked traces of albumin, specific gravity 1020. April 28, 1906, the dog died, having had general muscular spasms several times a day for the past week; death in tonic convulsion; weight, 7940 G.

Autopsy.—No edema of the body, but dilatation of superficial capillaries; no fluid accumulations in the pleura, pericardium or peritoneum. Heart distended and enlarged. Lungs deeply congested. Kidneys soft, swollen and congested.

Histologic Examination.—The heart muscles and aorta show no changes from normal structure. The lungs show intense engorgement with a few areas of pneumonic consolidation in what would correspond to the stage of red hepatization. There is no connective tissue increase in the lungs. The liver cells are poorly defined, take the stain poorly, and there are a few small areas of necrosis in the parenchyma. There is no increase in the connective tissue. The kidneys present the picture of severe chronic degeneration. The capsule is much thickened and there is an extension of the recently forming new connective tissue from the inner layers of the capsule into the cortex of the kidney. Here we find compression of the superficial tubes. The glomerular tufts are, for the most part, distended and the tuft cells increased in number. Elsewhere the glomeruli share in the general parenchymatous degeneration. It is difficult to find any normal tubules, straight or convoluted. The degeneration has not been of sufficient duration to allow of replacement fibrous formation, although small areas of round-celled connective tissue are found in the cortical layer.

ETHER.

The vasodilatation caused by ether is one of its marked effects on the vascular system, and its repeated use might be expected to cause some injury to the function of various tissues, as the result of the general low-

ering of blood pressure, apart from the accepted irritant effect it has upon the kidneys and lungs during and immediately after its administration.

PROTOCOL 2.

Dog.—Black and white male fox terrier; weight, 6100 G. Probation period from April 28, 1905, to Sept. 9, 1905. No albumin or casts in the urine; specific gravity ranged from 1028 to 1038. Respirations from 20 to 24, pulse from 90 to 100. Ether was administered by inhalation method at frequent intervals from Sept. 9, 1905, to March 24, 1906, the doses varying from 90 to 200 c.c., and the total amount used being 5590 c.c. The duration of the effect of the drug in each instance was from 20 to 60 minutes. The pulse was increased from 180 to 200, and the respiration to from 36 to 44 in the minute. Cyanosis did not occur, and the skin, though warm and pink, did not show any marked vasodilatation during treatment.

March 24, 1906: Weight, 7340 G.; in perfect condition; no albumin or casts in the urine.

Feb. 22, 1907: During the past year the dog has been in uniformly good condition, on the diet as described; no albumin or casts have been found in the urine; weight 7210 G.

July 19, 1907: Still in the best of condition; weight 7210 G.; no albumin or casts; killed by destroying medulla with a knife, i. e., by "pithing."

Autopsy.—No abnormal appearances in any organs.

Histological Examinations.—Heart, liver and aorta present no abnormal microscopic appearances. The kidneys show a marked chronic inflammation, characterized by moderate thickening of the capsule in a few places, with a slight increase of connective tissue cells from the surface of the capsule into the cortex of the kidney, and a free subcapsular vascular network. The cells of the glomerular tufts are increased in size and number, and the capsular cells are in some instances increased. There are numerous small areas of connective tissue of comparatively recent formation, and in no instance have they resulted in contraction of the tufts after a resulting atrophy. The tubular epithelium is swollen, but not degenerated. The appearance would suggest a chronic productive nephritis, resulting from chronic congestion.

CHLOROFORM.

Chloroform inhalation causes a fall in general blood pressure and, according to Thompson,[5] an increase of blood flow through the glomeruli of the kidney, a prolonged administration resulting in a vascular stasis in the glomerular vessels. In other words, aside from its effects as a protoplasmic poison, which chloroform has on all tissues, it causes a general low blood pressure throughout the body, and a greater or less congestion of the kidney according to the depth of the narcosis. Embley and Martin[6] explain the effect of chloroform inhalation from 1 to 3 per cent. vapor as due to a paralysis of the neuromuscular mechanism of the renal vessels, which they say accounts for most of the fall in general blood pressure always noted in chloroform narcosis.

5. Thompson: Brit. Med. Jour., 1906, i, 608.

6. Embly and Martin: Jour. Physiol., 1905, xxxii, 147.

PROTOCOL 3.

Dog.—Brown and white male fox terrier; weight, 6400 G. Urine, specific gravity, 1024; no albumin or casts. Normal respiration, 22; pulse, 90. Probation period from April 28, 1905, to Sept. 16, 1905; mange during the summer, cured by September 16. Chloroform was administered by inhalation from Sept. 28, 1905, to March 24, 1906, at frequent intervals. The dose varied from 30 to 40 c.c. at each treatment, the total amount used being 1280 c.c. The duration of the effect of the drug varied from 45 to 75 minutes at each treatment; the pulse was increased to 96 or 100; respiration decreased to 12 or 14 in a minute. Occasionally it was necessary to use artificial respiratory movements, with the dog removed from the box, to accomplish resuscitation from the occasional collapses, which the free use of chloroform sometimes brought on.

Feb. 1, 1906: Weight, 6770 G. Appears to suffer from some urinary irritation. Urine, specific gravity, 1044; heavy traces of albumin.

March 24, 1906: Weight, 8050 G. In fine condition; urine free from albumin and casts; specific gravity, 1055.

Nov. 22, 1906: Died; weight, 6040 G.; had been failing in strength for some time past; no mange. Except for an apparently enlarged heart there is nothing noticeable at autopsy except marked emaciation.

Histologic Examination.—Heart muscle, aorta and liver normal. Lungs show considerable collections of black granules surrounded by connective tissue. Many of the alveolar cells include foreign particles. The kidneys show swelling and hypertrophy of the tuft cells and some proliferation of the capsular cells about the glomeruli. The kidney capsule shows no changes. The tubules show a moderate cloudy swelling, and the lumen in some instances is filled with granular detritus. There is no new connective tissue formation.

AMYL NITRITE INHALATION.

Amyl nitrite acts directly on the muscular coat of the blood vessels and causes a wide dilatation. The formation of methemoglobin, which occurs rapidly, prevents the use of amyl nitrite over long periods and was the cause of death in one of the tests to be described. It was thought probable that repeated alterations in the general blood distribution of the body, caused by amyl nitrite, might affect the kidneys.

PROTOCOL 4.

Dog.—Brown and white male fox terrier; weight 7050 G. Urine, specific gravity, 1030; no albumin or casts. Normal respiration, 16; pulse, 96. Probation period from May 24, 1905, to Sept. 11, 1905. Amyl nitrite was administered at intervals from Sept. 11, 1905, to Feb. 6, 1906, in doses of from 2 to 7 c.c. each, the total amount used being 170 c.c., the effect lasting from 20 to 40 minutes. Vomiting, dizziness and apparently delirium occasionally accompanied recovery from the use of the drug.

Feb. 4, 1906: Urine free from albumin and casts; specific gravity 1050; weight, 6730 G.

Feb. 6, 1906: After being in the box ten minutes with a dose of 4.5 c.c. the dog collapsed and could not be resuscitated from the extreme cyanosis and urgent dyspnea which shortly terminated in death.

Autopsy.—This revealed a blanched surface, deep (methemoglobin) cyanosis of mucous membranes, muscles pale and purplish red, heart intensely engorged, lungs collapsed and pale, liver deeply congested, kidneys tense and deeply congested, stomach and bowels empty.

Histologic Examination.—The heart and lung specimens were spoiled in the hardening fluid and could not be cut. The liver shows general capillary distention and engorgement. The two kidneys appear intensely congested. The glomerular tufts are distended with blood. The tubules almost uniformly are separated from one another by capillary vessels full of red blood cells instead of appearing to be in direct contact which is usually the case, i. e., the entire capillary network of the kidney appears engorged without any change in the parenchyma or capsule. There is no new connective tissue formation. This picture of acute congestion would certainly be expected from the cause and manner of death.

PROTOCOL 5.

Dog.—White and brown mongrel male, 8350 G.; no albumin or casts in urine; specific gravity 1014. Probation period from June, 1905, to Nov. 4, 1905. Amyl-nitrite was administered from Feb. 8, 1906, to March 24, 1906, in doses of 3 c.c. each to a total of 50 c.c. The effects were similar to those observed in the dog of Protocol 4.

Feb. 26, 1907: Weight 8940 G.; trace of albumin, general condition good.

July 1, 1907: Weight 7500 G.; dog died after a period of gradual failure of appetite and nutrition without convulsions or other appearances of disease.

Autopsy showed no gross evidences of disease except an unusually flabby heart muscle and congested lungs.

Histologic Examination.—The heart, liver and lungs are normal. The kidneys show moderate thickening of the capsule, but no tendency to connective increase or the formation of wedges in the kidney parenchyma. There is distinct, though not extensive increase in the glomerular tuft cells, and in a few instances a flattening or atrophy of the capsular cells. The tubules are in some places markedly degenerated as shown by the granular and non-nucleated condition of the cells, the abundant granular detritus in the lumen, and the absence of clearly defined cell outlines. A few areas in the outer layer of the cortex show young round celled connective tissue formation.

SUMMARY A.

1. The inhalation of alcohol has caused chronic degeneration of the kidneys with a beginning connective tissue replacement.

2. The inhalation of ether has caused a chronic productive nephritis, in which we find a swelling of the tubular epithelium, increase in the size and number of the glomerular tuft cells and areas of connective tissue formation.

3. The inhalation of chloroform has caused some interference with the nutrition of the glomerular and tubular cells, resulting in a moderate swelling and degeneration.

4. The inhalation of amyl nitrite has caused in one instance death with marked visceral engorgement and intense renal congestment, and in another instance we observe a moderate degeneration of the tubular epithelium and a connective tissue formation.

5. The three dogs which had been subjected to alcohol, chloroform, and amyl nitrite inhalation a considerable time before their death, died under such conditions as to make one suspect an error in nutrition and elimination, and the pathologic findings, although not conclusive, sug-

gest that the condition of the kidneys was probably responsible for their deaths.

6. The facts that the four dogs, which survived the prolonged treatment by inhalation of the various drugs, gained in weight and maintained apparently excellent health up to the time the treatment was discontinued, and that the symptoms of failure in nutrition occurred some months later, argue for the probability that none of the drugs caused acute degenerative changes at the time of their administration, as they are known to do when given in large doses, but that the repeated disturbances of circulation which all these drugs effect resulted finally in the various grades of chronic degeneration, followed or not by chronic productive nephritis, which were found at autopsy.

B. EFFECT ON THE KIDNEY OF MECHANICAL INJURY OF ITS SUBSTANCE AND OF VARIOUS DRUGS INJECTED DIRECTLY INTO ITS SUBSTANCE.

ALCOHOL.

Alcohol was used in two dogs, in one in 50 per cent. strength and in the other in 25 per cent. strength, with the expectation that a coagulation of the kidney substance might occur at the site of the injection, which would so interfere with the nutrition of the kidney that a general nephritis would result.

PROTOCOL 6.

Dog.—White and black male fox terrier, weight 9110 G. Urine free from albumin and casts throughout a four-month probation period as described above. Between January 11 and 31, 1906, ten injections of 50 per cent. alcohol of 4 c.c. each were made into the left kidney. No albumin was found in the urine of this dog at any time.

Feb. 8, 1907: The dog died, weight 5880 G.; it had been failing in strength for some time past although taking large amounts of biscuits and water and not suffering from diarrhea or vomiting. No convulsions.

Autopsy.—Emaciation severe; right kidney pale, smooth, normal; left kidney deep purple, scarred and intimately adherent to the lumbar muscles. The heart, aorta, liver and lungs appear normal.

Histologic Examination.—The heart, aorta and liver appear normal. The lungs show slight capillary congestion. The right kidney has a normal capsule and parenchyma. The left kidney shows advanced and extensive, chronic inflammation, most severe at the point of dense renomuscular adhesions and extending in a wide area of obliterating connective tissue growth as deep as the pelvis of the kidney. In these regions, of which there are several, extensive destruction of the glomeruli and the tubules has occurred. Hyaline and granular material fills the tubules, the tubular epithelium being represented in many cases by a shrunken nucleus and a slender layer of cell bodies. The fibrous tissue is organized and dense, and what vessels have originally taken part in the active process of repair are now sharing in construction and obliteration, as in scar tissue. The kidney presents all stages of advanced productive nephritis, apparently as the direct result of the coagulation infarct which must have resulted at the time of the injection of alcohol into the kidney substance.

PROTOCOL 7.

Dog.—White and black fox terrier, female; weight after three months' probation period 9850 G. Urine, free from albumin and casts, specific gravity 1024. From Feb. 2 to Feb. 27, 1906, the dog received ten injections into the left kidney of 6 c.c. each of 25 per cent. alcohol.

Dec. 20, 1906: Weight 6300 G.; the dog has been failing for past four weeks, appetite is poor and diarrhea is present, lately increasing to general convulsive seizures.

Dec. 24, 1906: Died. Weight 6000 G.

Autopsy.—Lungs show hypostatic congestion at the bases; the heart and vessels appear normal; right kidney normal; left kidney adherent to lateral abdominal wall; kidney substance appears normal.

Histologic Examination.—Heart and liver show no variations from normal. Right kidney appears normal. Left kidney shows moderately thickened capsule and a few areas of connective tissue infiltration from the capsule inwards. There is no degeneration or inflammatory process throughout the kidney parenchyma.

ADRENALIN.

Adrenalin was used in one dog in the expectation that some distinct difference between the resulting constriction of vessels locally and the effect of alcohol on the kidney might appear.

PROTOCOL 8.

Dog.—White female mongrel; weight 7150 G. No albumin or casts found after four months' probation period. Between Jan. 11, 1906, and Feb. 27, 1906, nineteen injection of 3 c.c. each of adrenalin chlorid solution (1 to 1000) were given into the left kidney.

April 18, 1906: The dog died suddenly without having been ill so far as could be observed. Weight 8200 G.

Autopsy.—The skin and mucous membranes were very pale, the viscera were deeply colored, but apparently not congested. The heart appeared enlarged and distended with dark venous blood. A small amount of pericardial fluid was found. The lungs were collapsed and congested.

Histologic Examination.—The two kidneys appear the same except for the lesions made by the needle in the left kidney; its parenchyma and capsule show injury. In both kidneys the capsule, glomeruli and tubules are normal except in the immediate vicinity of the lesions just noted. The lumen of the tubules appears empty or containing a small amount of cell detritus. The heart, aorta, liver and lungs are normal.

SODIUM CHLORID.

Normal salt solution, 0.8 per cent., was used as a control to see what effect on the kidney the injection of an isotonic non-toxic solution would have.

PROTOCOL 9.

Dog.—Black and white female fox terrier. Weight 8180 G.; no albumin or casts in urine after four months of probation period; specific gravity 1020.

Between Jan. 11 and Feb. 27, 1906, nineteen injections of normal salt solution of 6 c.c. each were given into the left kidney.

March 24, 1906: In fine condition, no albumin.

Feb. 25, 1907: Weight 9800 G.; in fine condition, no albumin.

July 19, 1907: Killed by destroying the medulla by pithing. Weight 7940 G.; active and alert though thin.

Autopsy.—Left kidney showed an area of thickened capsule where it was adherent and contracted. Right kidney and the other organs are normal.

Histologic Examination.—The heart, aorta, liver, and right kidney present wholly normal structure. The left kidney shows much thickened capsule with areas of newly forming connective tissue in the cortex and as deep as the medullary portion, obliterating the tubules and resembling the wedges of productive connective tissue resulting from decapsulation of the normal kidney, or the kidney in chronic nephritis, with the exception that the areas in the kidney under consideration are long, narrow and confined within pretty distinct limits, suggesting strongly that these areas represent the scar tracts left by the penetrating needle.

MECHANICAL INJURY.

Two dogs were used to test the effect of the mechanical injury of inserting a hypodermic needle in the renal parenchyma.

PROTOCOL 10.

Dog.—White and brown female terrier, weight 6130 G.; at the end of a two-months' probation period. No albumin or casts.

Between Jan. 11 and 31, 1906, the hypodermic needle was passed into the left kidney nine times.

January 31: Being in doubt as to the accuracy of my manipulation of the needle, the dog was lightly chloroformed with the intention of locating the needle more exactly in the kidney. Unfortunately the dog died under the narcotic, but the needle was found to have been placed directly into the kidney.

Autopsy.—Nothing abnormal was found except a few recent hemorrhagic areas in and beneath the kidney capsule.

Histologic Examination.—No variations from normal were found except slender tracts of young connective tissue in the left kidney.

PROTOCOL 11.

Dog.—Yellow mongrel female. After three months of probation period, weight 6550 G.; no albumin or casts.

Between Feb. 1, and 27, 1906, the left kidney was needled twelve times.

Feb. 14, 1907: After a period of severe mange accompanied by diarrhea and loss of weight to 3600 G. the dog died.

Autopsy.—No macroscopic changes noted except total absence of fat throughout the body; kidneys showed no gross lesions.

Histologic Examinations.—The liver specimen was excessively hardened and could not be sectioned. The heart muscle and aorta appear normal. The lungs show congestion and in a few small areas, the alveoli are filled with blood though not presenting the appearances of inflammatory consolidation. The left kidney shows a thickened capsule with dense connective tissue pressing irregularly on the cortex and in places invading it. There is new connective tissue formation in several narrow areas deep in the parenchyma of the kidney, presumably the lines of needle puncture. Except for these evidences of injury there is no appearance of nephritis, the glomeruli and tubules appearing normal.

SUMMARY B.

1. Injections of alcohol into the kidney substance cause connective tissue increase in the kidney, resulting in an interference with the nour-

ishment of the tubules and the glomeruli, which resembles the milder grades of chronic productive nephritis.

2. Adrenalin injected into the kidney substance is not of itself the cause of any circulatory or inflammatory changes locally, although the injury incident to injection shows a resulting scar.

3. The use of the hypodermic needle without any injection fluid, and the use of normal saline injections into the kidney substance, are both followed by the formation of connective tissue tracts in the kidney which resembles the replacement fibrosis which occurs in chronic nephritis. That is, the structural changes observed in nephritis in man is imitated, but there is no general distribution of the connective tissue throughout the kidney such as appears when there is a true inflammatory process.

C. EFFECT ON THE KIDNEY OF INCREASED VISCOSITY OF THE BLOOD DUE TO THE ADDITION OF GELATIN TO THE BLOOD STREAM; AND OF SOLUTIONS OF ADRENALIN CHLORID AND OF ACETATE OF LEAD.

GELATIN.

In spite of the fact that increased viscosity as a possible cause of renal disease has been examined and found wanting by Hirsch and Beck,[7] it seemed possible that if gelatin were added to the blood over a period of days some circulatory or structural changes might be found in the kidney. Opitz[8] has found that gelatin solutions increase the viscosity of dog's blood promptly and to a considerable degree.

PROTOCOL 12.

Dog.—Black and white mongrel male, weight 10000 G. After three months' probation period; no albumin or casts in urine; specific gravity 1048.

Between Jan. 18 and Feb. 27, 1906, nineteen injections of 5 per cent. gelatin in water of 6 c.c. were given into one of the superficial veins of the dog's legs.

No albumin or casts were found at any time in the urine of this dog, and on July 19, 1907, he was killed by "pithing." In fine condition, weight 9320 G.

Autopsy and histologic examination revealed no variations from normal in any tissue.

ADRENALIN CHLORID.

The use of repeated doses of adrenalin chlorid in the general circulation causes temporary vasoconstriction in all the vessels of the body except those of the lungs, a great contraction of the kidney vessels and a temporary decrease in the secretion of urine. This is a matter of common laboratory observation and has been made the subject of exact record recently published by Schlayer and Hedinger.[9] Such a phenomenon,

7. Hirsch and Beck: Deutsch. Arch. f. klin. Med., 1902, lxii, 560.

8. Opitz: Arch. f. d. ges. Physiol., 1900, lxxxii, 447.

if repeated, might be expected to cause some permanent alteration in the blood supply, function or structure of the kidney.

PROTOCOL 13.

Dog.—Unfortunately the dog used for this test was infected after seventeen injections of 3 c.c. each of adrenalin chlorid solution, and death resulted from pyemia a few days later.

Histologic Examination.—The histologic picture of the kidneys was that of acute degeneration with hemorrhages in the parenchyma. No conclusions could be drawn from this test and time was lacking to repeat it.

ACETATE OF LEAD.

As a control test to have some recognized type of experimentally produced nephritis to compare with the lesions produced by the other procedures used in this study, the intermuscular injection of solutions of acetate of lead was adopted.

PROTOCOL 14.

Dog.—Feb. 22, 1906: White and black terrier, male, weight 9850 G. After three months' probation period the urine showed no albumin or casts. Over a period of two months injections of 1 c.c. each of a 10 per cent. solution of acetate of lead were given in the muscles of the legs.

August 14, 1906. For the past two weeks, convulsions and considerable loss of weight.

Autopsy.—Except for the smallness and hardness of the kidneys no variations from normal were found.

Histologic Examination.—The heart muscle shows no abnormal structure. The section of the aorta shows no thickness of the elastic coat, no separation of the elastic fibers and no infiltration or degeneration of the endothelial coat. The vasa vasorum appear healthy. The liver appears normal. The kidneys show no change in the capsule as to their thickness or vascular supply. The glomeruli are distended, everywhere filling the capsule of Bowman completely. The tufts appear to be the seat of active cell proliferation. The capsular cells are not increased. There is no atrophy, but a uniform swelling of the glomerular tufts. The tubular epithelium fills the lumina almost everywhere. There is little cellular detritus in the tubules. The cells lining the straight and convoluting tubules are swollen. There are occasional hemorrhages among the tubules, in some of which absorption is in process; others are evidently recent. The condition resembles that of a mild chronic degeneration more than a chronic productive nephritis which would probably result if the poisoning had been more severe or the period of observation longer.

SUMMARY C.

1. Increased viscosity of the blood due to the presence of gelatin does not affect the kidneys.

2. Lead acetate solution caused a chronic degeneration of the kidneys.

3. Although the test with adrenalin was inconclusive, this failure is not of vital importance, as Loeb[10] found that inflammatory processes

9. Schlayer and Hedinger: Deutsch. Arch. f. klin. Med., 1907, xc, 1.

10. Loeb: Am. Jour. Med. Sc., 195, cxxx, 665.

never resulted from adrenalin injections, the effect being degeneration processes in various stages.

DISCUSSION.

The function of the healthy kidney depends on three main classes of factors. Of paramount importance is the blood flow through the kidney, which may vary in its pressure, its rate, and the size of the vascular path to and from the glomeruli and the convoluted tubules. The quality of the blood reaching the kidney is important, as it has been shown to affect renal secretion through variations in its chemical composition, its temperature, its viscosity, and its osmotic pressure. Direct and reflex nervous stimulation also has been shown to alter the activity of the renal epithelium.

When we find errors in the function of the kidney we must look to some alteration of the normal nerve control, or to some defect in the quality of the blood, or to some error in the character of the circulation. Even grave defects of function may exist and persist even for long periods, as, for example, the excessive diuresis in diabetes insipidus, without necessarily being accompanied by any appreciable alteration in the secreting cells or in the blood vessels of the kidney.

Very considerable alteration of the kidney structure is frequently found without any suspicion having been aroused of faulty function of the kidney, either by the general health of the individual before death, or by exact analysis of the urine. It is apparent, then, that the experimental study of chronic diseases of the kidney can not be expected to give a full answer to the question of etiology.

Histologic examination of kidneys often reveals advanced structural changes which have not been suspected by a faulty function during life.

Urinary analysis fails to supply an altogether reliable source of information as to changes of renal structure, and still less in regard to temporary errors in the function. Blood analysis, as by cryoscopy, supplements our other means of diagnosis, but is not invariably sufficient to point to the exact character or degree of renal disease.

Delafield[11] tersely states: "Any educated physician will now admit that albumin may be absent with kidney disease and present without it."

A recent test, applied by Schur and Weisel,[12] which, it is claimed, will detect the presence in the blood of nephritics of a substance exerting the mydriatic effect of adrenalin on the frog's eye, may add to our means

11. Delafield: Lectures on the Practice of Medicine, New York. Part I, 8-17; Part IV, 412-496.

12. Schur and Weisel: Wien. klin. Wchnschr., 1907, xx, 699.

of diagnosis. They say that the sera of normal people do not give this reaction.

We may expect as much information from the accumulation of clinical data as from animal experimentation.

A summary of the procedures which have been adopted in animal experimentation shows only a few which have actually resulted in the approximation of lesions such as are found in chronic nephritis in man. Ophüls[13] considers that Ehrlich[14] and Levaditi[15] have produced chronic nephritis by the use of vinylamin. Paessler and Heineke[16] obtained chronic nephritis by operative removal of large parts of the kidney substance. Posner[17] quotes Orth as having obtained nephritis in rabbits by subcutaneous bruising of the kidney. Similar lesions have been produced in the present study by coagulation infarcts due to the injection of alcohol into the kidneys. These lesions, due to operative removal, chemical or mechanical injury, and subsequent fibrous repair, are all similar to the cases of chronic productive nephritis reported in the experimental results of Johnson,[18] Emerson, [19] and Osmoloffski[20] after decapsulation of the kidney in animals.

Among the means which have been used to cause the production of interstitial changes in the kidney are aloin, boracic acid, cantharidin,[21,9] potassium chlorate, chromic acid, potassium bichromate,[22] salts of lead,[15] mercury[9] and arsenic,[9] oxalic acid, oxamid, sulphuric acid, the toxins of the pneumococcus and of the diphtheria bacillus,[9] uranium nitrate, theocin,[20, 23] excessive amounts of chlorids[24] and phosphates,[25] alcohol[26] and nephrotoxic serum.[3]

Caro[27] found nephritis in cats from five to eight days after experimental removal of the thyroid.

Of all these procedures, the use of small doses of the salts of lead is

13. Ophüls: Jour. Am. Med. Assn., 1907, xlviii, 483.
14. Ehrlich: Internat. Beitr. z. inn. Med., 1902, i, 647.
15. Levaditi: Arch. internat. de pharmacod., 1901, viii, 45.
16. Paessler and Heineke: Verhandl. d. deutsch. path. Gesellsch., Berlin, 1905, p. 99.
17. Posner: München. med. Wchnschr., 1906, liii, 531.
18. Johnson, H. A.: Ann. Surg., Philadelphia, 1903, xxxvii, 592-601.
19. Emerson, H: Am. Jour. Med. Sc., 1904, p. 692.
20. Osmoloffski: Russk. Vrach, 1903, ii, 801.
21. Brodzki: Berl. klin. Wchnschr., 1906, xliii, 906.
22. Blank: Ztschr. f. klin. Med., Berlin, 1906, lx, 400.
23. Heineke and Myerstein: Deutsch. Arch. f. klin. Med., 1907, xc, 101.
24. Weber: Arch. f. exper. Path. u. Pharmakol., 1905-6, liv, 1.
25. Leopold: Ztschr. f. klin. Med., 1906, lx, 481.
26. Friedenwald: Jour. Am. Med. Assn., 1905, xlv, 780.
27. Caro: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1907, xvii, 447.

the only one which is known to produce regularly a chronic nephritis in man and animals. All the other procedures have resulted in degeneration of the kidney of an acute or chronic character, or have caused but temporary lesions which leave no permanent effect on the kidney parenchyma.

We have, then, two methods which caused what resemble the lesions, but not the clinical picture of chronic nephritis in man: the use of lead salts and the formation of scar tissue within or on the surface of the kidney. It is true that neither of these can be considered as frequent causes of nephritis in man.

The causes usually included in the etiology of chronic nephritis in man come under four headings:

1. Infectious diseases: scarlet fever, diphtheria, pneumonia, typhoid fever, tuberculosis of any part of the body, septicemia, and erysipelas.

2. The poisons of gout, rheumatism, syphilis, and lead.

3. Vices of appetite; the excessive use of nitrogenous and other stimulating foods and drinks.

4. Errors persistent, or frequently repeated, in the circulation: cardiac disease; exposure to wet and cold; muscular fatigue; attacks of acute or chronic congestion and degeneration of the kidney; attacks of acute exudative nephritis; mental worry and anxiety.

Loeb[28] would add that non-nephritic albuminuria leads in a high percentage of cases to a real nephritis, and his reasoning to this end is important. He finds that orthostatic albuminuria is, in a majority of cases, of cardiovascular origin. A diminished blood flow through the kidney with increased pressure in the renal vein is the cause of renal hyperemia. This condition is often due, according to Krehl,[29] to the "cor juvenum."

Again, J. Rose Bradford,[30] although denying that all cases of orthostatic albuminuria lead to a chronic lesion, explains the increase of albuminuria in a convalescent from acute nephritis when assuming the erect posture, by the less advantageous circulation which the kidney obtains in this position.

Delafield[11] gives cases to show that albuminuria appears after prolonged exertion owing to a congestion of the kidneys. After cessation of the exertion the albumin regularly disappears within a few hours.

28. Loeb: Deutsch. Arch. f. klin. Med., 1905, lxxxv, 348; lxxxiii, 452.

29. Krehl: Deutsch. med. Wchnschr., 1905, xxxi, 1872; Deutsch. Arch. f. klin. Med., 1906-7, lxxxviii, 351.

30. Bradford: Brit. Med. Jour., 1907, i, 725.

Fothergill[31] (1887) states that the knowledge of that time warranted the conclusion that "the waste-laden condition of the blood causes a contraction of the tiny arterioles producing high tension. The sustained high arterial tension sets up atheromatous changes in the arterial walls, and from this spring a number of maladies." While this idea has much to support it and has been widely accepted up to the present time, the studies of Slade,[32] of Sollmann[33] and of Opitz[8] suggest that this conception is wrong, and that in the case of meat extractives, although there is a general contraction of all smooth muscle tissue, a vasodilatation of the kidney vessels occurs.

Slade found that: (1) Muscle extracts increased the rate and activity of the heart. (2) Blood vessels are constricted. (3) Plain muscle of the whole body shows increased movement. (4) In the form of beef tea, moderate diuresis accompanied by vasodilatation of the kidney occurs.

Sollmann finds that if the viscidity of the blood is increased a dilatation of the renal arteries and veins occurs in the perfused excised kidney, and that blood has a dilator effect on the vessels of the excised kidney.

Opitz finds that a heavy meat diet materially increases the viscosity of the blood in dogs.

It would be easier to accommodate this series of experimental results in a theory which postulated a dilatation of the kidney vessels at a time when the other vessels of the body are contracted, rather than in any supposition which demands that the kidney must share uniformly in the contraction of the blood vessels of the body at large. When there is an increase in proteid extractives in the blood, the viscosity of the blood is increased, and if these substances remained in the body they would do harm. The stimulus of these harmful substances is apparently responded to by two circulatory changes, a constriction in the vessels of the body at large, causing high blood pressure, and a dilatation of the vessels of the kidney. These alterations in the circulatory distribution would at once put the kidney in the best possible condition to secrete, i. e., a wide capillary path and high general blood pressure, providing a maximum amount to pass through the kidney in a given time.

That there is a general vasoconstriction and general rise of blood pressure is a common observation in nephritis, but it can not at all be claimed that constriction of the renal vessel occurs coincidently, and it is

31. Fothergill: Vaso-renal Changes versus Bright's Disease, New York, Putnam, 1887.
32. Slade: Jour. Physiol., 1907, xxxv, 165.
33. Sollmann: Am. Jour. Physiol., 1905, xiii, 24.

to be noted particularly that the splanchnic blood vessels do not necessarily exhibit vasomotor changes identical with those of the skin and muscles. The effect of cold on the surface of the body is to contract the vessels of the skin, and this is usually accompanied by diuresis, as Dubois and Butruille[34] have recently demonstrated so successfully, and in this case the increased activity of the kidney must be supposed to be due to the presence of more blood in the kidney, which can not itself be directly affected by the cold which constricts the vessels of the surface of the body.

As Graupner[35] says, high blood pressure occurs in nephritis as soon as substances are retained that should be excreted, and it drops spontaneously as soon as the renal function is re-established. Or it may be said that an increase in the substances to be excreted puts more work on the normal kidney. Increased function demands increased blood flow. This is accomplished under physiologic conditions by a rise in blood pressure due to increased heart action and vasoconstriction, and we may suppose to a dilatation of the renal vessels, although a positive proof of this is not at hand.

Morse[36] thinks that a certain proportion of cases of chronic nephritis in man may be due to the action of chemical substances produced by bacteria, inasmuch as the human kidney is more or less constantly exposed to the action of such substances.

Grund[37] finds that cystoscopy, ureteral catheterization, and stone in the bladder cause reflex interference with renal functions to such a degree as to lead to grave errors in the functional powers of the kidney, as well as to difficulties in drawing reliable conclusions from urinary analysis under such conditions.

Carter,[38] in a critical and experimental study of the etiology of nephritis in Galveston, Texas, concludes that the excessive use of meats in a warm climate and carelessness in recognizing and treating infectious diseases, and not the climate *per se*, are responsible for the prevalence of kidney disease in that region.

v. Homeyer,[39] in a study of nephritis in the German army from 1884 to 1904, found the commonest cause of acute nephritis to be the infectious diseases scarlet fever, tuberculosis and diptheria. Second in fre-

34. Dubois and Butruille: Echo méd. du nord, 1907, xi, 253-255.
35. Graupner: Berl. klin. Wchnschr., 1907, xliv, 453.
36. Morse: Jour. Exper. Med., 1896, i, 613.
37. Grund: München. med. Wchnschr., 1906, lxii, 1803.
38. Carter: Med. News, New York, 1904, lxxxv, 919.
39. Homeyer: Ueber die Haufigkeit der Nierenkrankheiten in der deutschen Armee 1884-1904, Inaug. Diss., Munich, 1907.

quency as a cause of acute nephritis he found to be chilling and wetting of the body, as by sleeping on the damp ground. He found that chronic nephritis was often traceable to chilling, and excessive bodily exertion to the degree of fatigue, especially in men who had passed through an acute nephritis at an earlier date.

Delafield says,[11] "As soon as the blood accumulates in the veins to any considerable extent, the kidneys suffer. One of three things regularly happens to them: either a chronic congestion, chronic degeneration or chronic nephritis is developed." And, again: "The same mechanical obstructions to the circulation—heart disease, pleuritic effusions, etc.—which produce chronic congestion can, instead of this, produce chronic degeneration."

It must be apparent that Councilman's[40] conclusion is correct: that kidney disease is not an entity, but that the kidney is secondarily affected.

If we examine the causes of nephritis as they have been outlined in the four classes above, it will be noticed, I think, that there is one important factor either constituting the entire cause, as commonly accepted, or playing an important part, if not an usually accepted part, in each instance. I have reference to circulatory stagnation in the kidney. In the infectious diseases the exact physiologic effect of the several bacterial toxins has not been completely studied. We have enough clinical data, however, to supplement the few experimental results that are available.

The work of Paessler and Romberg[41] showed that the cause of death in diphtheria and in experimentally produced pneumonia was due, not to cardiac failure, but to a toxic paralysis of the peripheral or central vasomotor control, resulting in vascular stasis.

In typhoid fever[42] and tuberculosis[43, 44, 45] low blood pressure exists for long periods, and there is some experimental proof that the toxins of the tubercle bacillus, at least, have a marked vasodepressor action.

In streptococcus infections, as septicemia, erysipelas, and we might almost say in scarlet fever, the uncomplicated results on the circulation

40. Councilman: Jour. Am. Med. Assn., 1906, xlvi, 81.
41. Romberg and Paessler: Arch. f. exper. Path. u. Pharmakol., 1899, xliii, 283.
42. Janeway, T. C.: Am. Jour. Med. Sc., 1907, cxxxiii, 50.
43. Regnault: Le cœur chez les tuberculeux, Paris, 1899.
44. Arloing, Rhodet and Courmont: Cong. p. l'étude de la tuberculose, Paris, 1891, ii, 29.
45. Charrin and LeNoir: Compt. rend. Soc. de biol., Paris, 1893, v, series 9, p. 769.

are those of low blood pressure, the pressure not rising in scarlet fever until albuminuria is established.

In nephritis following gout, rheumatism, syphilis and chronic lead poisoning, the case is not so clear, but it must be kept in mind that in all four of these instances there is a marked tendency to fibrous tissue formation, especially in the walls of the blood vessels. The high blood pressure which results from chronic arteritis may be preceded by stages of insufficient pressure which we fail to recognize clinically.

Where we are considering what I have called vices of appetite or habit it will be noticed that the substances mentioned are all classed commonly as stimulants, in that they produce temporary increase in cerebral activity. Excess of activity is compensated for physiologically by relaxation and rest, and I believe that it is not too much to claim that in all instances where abundant use of meat and stimulants is indulged in the circulation undergoes considerable depression after the immediate effect of the increased activity has passed. The dilated facial capillaries of the hearty eater and drinker are an evidence of vascular stasis following frequently repeated over-stimulation.

What I believe can be shown to be the entire cause of chronic nephritis in many cases is the result of the various disturbances included in the last group. Exposure to wet and cold cause a central congestion by peripheral constriction in the skin and muscles. Muscular exertion, if carried to the degree of fatigue, results in general relaxation of vascular tone. Previous attacks of acute exudative, acute congestive and acute degenerative nephritis leave the kidney especially susceptible to subsequent congestion, and are, if repeated, sufficient cause for persistent congestion and nephritis. The pale surface and tightened artery of the man under the strain of business or professional cares is familiar, and every such picture presents an instance of physiologic fatigue, in which the vasomotor center is being excessively stimulated and the heart is pumping against unnecessarily high resistance. The result is visceral congestion.

Congestion causes functional inadequacy in any tissue. Inadequacy of renal function causes, among other things, according to Leopold,[24] a retention of chlorids and phosphates in the blood, and the presence of an excess of chlorids and phosphates in the blood may cause albuminuria, which of itself is a sign of faulty function and faulty circulation.

The improvement in chronic nephritis under such treatment as is directed chiefly to maintaining the circulation at a constant level of efficiency is an indication that circulatory error probably shared in the

causation of the disease. Webster's[46] summary of the treatment of chronic nephritis may properly be taken as a type of treatment that would be generally accepted. He advises dietetic moderation beyond the point of supplying ample food to carry on bodily functions and maintain nutrition; woolen clothing, bathing, open-air life where there are no rigors of climate; exercise never to the point of fatigue, to maintain the cardiovascular equilibrium at its most efficient point.

The suggestions with which Janeway[42] supplements Loeb's[27] theory of the causation of increased arterial tension and cardiac hypertrophy in chronic nephritis show a similar conviction to the one I have expressed.

"In chronic kidney disease we must look for some cause of the increased pressure. May it not be that the conditions of the circulation in the kidney are such that an increased pressure must be maintained in order to accomplish the necessary amount of secretion? Any local or general cause of slow blood flow, or low blood pressure, or congestion or stagnation in the renal circulation would at once be met by an increase in general blood pressure. If this is continually persisted in, it is entirely conceivable that it might become permanent. Increased arterial pressure is a symptom, or, more truly, a proof of the body's defensive action against disease."

Or as Loeb himself says: "Cardiac hypertrophy and increased blood pressure are compensatory reactions, occurring when the glomeruli are imperfectly supplied with blood, because inflammation or stasis has allowed too low a capillary pressure for proper filtration."

Schlayer and Hedinger[9] note that every injury to the renal vessels resulting in an error of circulation expresses itself in a diminution of diuresis.

CONCLUSIONS.

From experimental results it would appear that interference with the blood supply of the kidney can be accomplished by means of chemical injury to the renal parenchyma, and that the process of repair which ensues may involve such a destruction of secreting tissue as to cause the death of the animal.

From the experimental use of general vasodilators, it appears that the kidney suffers at least mild grades of degeneration, which may be due, not to the specific renal irritation of the drugs employed, but to the defective blood supply which frequently repeated vascular relaxation causes.

From an analysis of the accepted causes of chronic nephritis in man it is evident that many of them have as a common factor a more or less

46. Webster: Am. Jour. Med. Sc., 1907, cxxxiii, 271.

severe and prolonged stagnation in renal blood supply, and, although this factor is often accompanied by the presence of irritants which we recognize as injurious to the kidney tissue, insufficient blood supply alone will cause, first, an error in the function and later an alteration in the structure of the kidney.

As convincing proof of the true cause or causes of chronic nephritis in man is not present, we must perforce accept as a theory one which will account for most of the known facts. Loeb's explanation of the probable sequence of the circulatory events coincident with the course of chronic nephritis in man might reasonably be supplemented by an explanation of the etiology of nephritis which recognizes as a frequent, if not an invariable factor, deficient renal circulation. Faulty function always results from deficiencies of blood supply and if the defects persist or are frequently repeated faulty structure results. In the case of the kidney, the fault in its function resulting from the altered structure in chronic nephritis will cause much or little disturbance in the body at large according to the degree of circulatory compensation which can be maintained. Cardiac disease, bacterial toxins, and metabolic waste products are probably the causes of the errors in circulation which cause, first, faulty function in the kidney and, finally, chronic nephritis.

If this theory of etiology is supported by subsequent study, its application to the prevention of nephritis might strengthen existing efforts to check the spread of infectious disease, and to urge moderation in the habits of over-stimulation and over-work, which are prominent in present day life in large centers of population.[47]

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47. In addition to the above, the following references will be found of interest: Barr: Brit. Med. Jour., 1907, i, 725. Georgopulos: Ztschr. f. klin. Med., Berlin, 1906, lx, 411.. Josué: Presse méd., 1907, xv, 233. Lutheus: Arch. f. exper. Path. u. Pharmakol., 1906, lv, 116. Paessler: Samml. klin. Vortr., 1906, new series, No. 2, p. 408. Paessler and Rolly: Deutsch. Arch. f. klin. Med., 1903, xvi, 217. Riegel: Ztschr. f. klin. Med., Berlin, 1884, vii, 260. Thayer: Am. Jour. Med. Sc., 1904, lxxvii, 391.

THE PREVENTION OF TROPICAL ABSCESS OF THE LIVER BY THE EARLY DIAGNOSIS AND TREATMENT OF THE PRESUPPURATIVE STAGE OF AMEBIC HEPATITIS.*

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During the last seven years I have enjoyed most exceptional opportunities for studying tropical abscess of the liver in Calcutta, and have now arrived at the conclusion that the disease can and should be prevented altogether in the great majority of cases. The following are briefly the steps by which I have reached this position:

In 1902[1] I published a paper on tropical, or amebic, abscess of the liver and its relationship to amebic dysentery, in which I gave tables to show that I had found living amebas in scrapings from the walls of 35 out of 37 consecutive liver abscesses, the two negative results being in those not examined until twelve or more days after the abscess had been opened and drained. Further, two-thirds of the abscesses, when first opened, were sterile as regards the presence of bacteria. Kruse and Pasquale had previously found amebas in only 6 out of 15 cases examined. I also showed that when both a clinical history and a postmortem record were available, in over 90 per cent. of the cases dysentery was found to be associated with the liver abscess, and in 95 per cent. of these there was evidence that the dysentery had preceded the formation of the abscess, while it was always, in my experience, of the amebic variety. I, therefore, concluded that the large tropical abscesses (as opposed to those due to suppuration in the portal veins or in the bile ducts) were always due to the *Amœba dysenterica*, and secondary to amebic dysentery, although the latter might often be of a latent nature, giving rise to no typical dysenteric symptoms during life, but revealing itself in the form of a few amebic ulcers found postmortem, usually high up the large bowel in the cecum or ascending colon.

In a second paper[2] in 1903 I gave an account of amebic dysentery in India and discussed the formation of amebic abscess of the liver. In 1905[3] I dealt with the value of leucocytosis in the early diagnosis of

* Read at the fifth annual meeting of the American Society of Tropical Medicine, held at Baltimore, March 28, 1908.

1. Brit. Med. Jour., Sept. 20, 1902.
2. Brit. Med. Jour., June 6, 1903.
3. Brit. Med. Jour., 1905, ii, 1291.

amebic abscess and pointed out that, although occasionally an attack of acute hepatitis with leucocytosis may clear up without suppuration occurring, yet, if such cases are followed up, sooner or later an abscess of the liver nearly always forms. I also narrated a case of acute hepatitis with leucocytosis, which cleared up under large doses of ipecacuanha.

In 1906[4] I published two cases of amebic abscess of the liver successfully treated by aspiration and injection of the soluble bi-hydrochlorid of quinin, without drainage, having found that the amebas in thick liver abscess pus could readily be killed by that drug in a strength of from 1 in 100 to 1 in 500, a method which has since proved effective in other hands, especially in early deep-seated abscesses, although it fails in many more advanced cases.

While on the lookout for the early stages of the disease for this line of treatment, I met a number of cases of fever with leucocytosis and symptoms of acute hepatitis, in some of which aspiration failed to reveal any abscess. They yielded, however, very rapidly to full doses of ipecac, thus showing that the increase of the leucocytes takes place before actual suppuration has taken place and sometimes many days earlier. Last year (1907) I published[5] a series of such cases which were rapidly cut short in the presuppurative stage by the ipecac treatment, which may be briefly summarized as follows: Fifteen cases were met in the Calcutta European General Hospital during twelve months. In only three was there a clear history of dysentery or symptoms of it while in the hospital, and they lost their fever and hepatitis after two to four days' ipecac treatment, although they had previously suffered from fever for 15, 34 and 41 days, respectively, and one had been aspirated for liver abscess with a negative result. In three more cases of acute hepatitis without dysentery not treated by ipecac, the fever subsided only after 34 to 49 days. In five similar cases treated with ipecac the fever subsided in 1 to 6 days, although it had previously persisted for 13 to 50 days, one patient having been aspirated for liver abscess with a negative result. Lastly, there were three cases of fever with no signs of either dysentery or hepatitis, other than very slight painless enlargement of the liver, but with leucocytosis of the same type as in the other cases, namely, without very marked increase of the polynuclears (usually from 70 to 80 per cent.). They had suffered from fever for 35, 45 and 53 days, respectively, but it ceased in two to fifteen days under ipecac treatment. This is the class of case in which a large, deeply-seated, fibrous-walled

4. Brit. Med. Jour., June 16, 1906, i.

5. Practitioner, Lond., 1907, lxxviii, 776; Tropical Fevers in the Tropics (Oxford Medical Publications).

abscess of the liver forms very insidiously with irregular intermittent fever, commonly treated as malarial, but with no very obvious signs of hepatitis until a very late stage. Two of the above fifteen cases relapsed and returned to the hospital 4 and 7 months later, respectively, each with an amebic abscess of the liver.

When dysentery is present and complicated by hepatitis, ipecac is advised by Sir Patrick Manson and other authorities, but at the time the above paper was published I was unable to find any recent writer who recommended large doses of ipecac for hepatitis when not accompanied by dysentery, although several of the older Indian authors, especially McClean and Norman Chevers, strongly urged its use in such cases also. The considerations which led me regularly to adopt this treatment were:

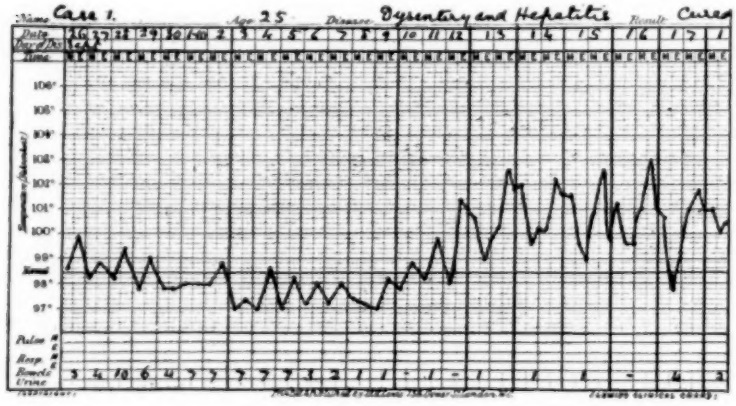

Chart 1—Case 1.

First, finding dysentery associated with 90 per cent. of tropical abscesses of the liver, and, second, the fact above mentioned that in many patients dying of liver abscess, without history or symptoms of dysentery, amebic ulcers are found postmortem in the upper part of the large bowel. I, therefore, regarded hepatitis accompanied by leucocytosis as an indication of the presence of latent amebic ulceration of the large bowel, which indicated large doses of ipecac for its cure. The results of this treatment, both those mentioned above and subsequent ones, have been so successful that during the last two years no instance of liver abscess developing while the patient was in the European General Hospital, Calcutta, has occurred, although a few patients have been admitted with an abscess

already formed. On the other hand, a number of very acute hepatitis cases have cleared up under ipecac after an abscess had been suspected, and in five instances also sought for in vain with an aspirating needle.

REPORTS OF CASES.

The following three examples, which have occurred within the last two months, will serve to illustrate the value of this method of early diagnosis and treatment:

VERY ACUTE HEPATITIS CLOSELY FOLLOWING ON DYSENTERY RAPIDLY CURED BY IPECAC.

CASE 1.—A European, male, aged 25, was admitted for dysentery of six weeks' duration, passing about six stools daily containing blood and mucus, without pain or straining. He was treated with a castor oil mixture and creolin

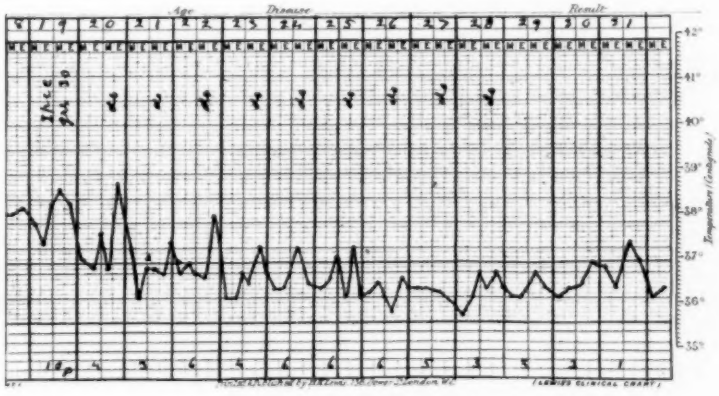

Chart 1—Case 1—Continued.

enemas, and the blood and mucus disappeared from the stools after ten days. Seven days later (September 11) he began to have pain in the hepatic region and in the right shoulder, and his temperature, which had previously been slightly subnormal, began to rise (Chart 1). The liver dulness was not increased, extending from the sixth rib to the costal margin. The pain continued to be severe, and on the 13th the breath sounds were noted to be weak at the base of the right lung. Morphia was being given for the pain, and ten grains of quinin three times a day for the fever. On the 15th there was profuse sweating, while the liver dulness now extended up to the fifth rib. Five leeches applied over the liver relieved the pain somewhat. On the 16th the right lower chest was observed to be moving less than the left, and on the 18th *x*-rays showed that the diaphragm on the right side was quite motionless, while there appeared to be a slight shadow in the right lobe of the liver. Abscess of the liver was, therefore, diagnosed. As, however, there had been recent dysentery, which had not been treated with full doses of ipecac, the physician in charge of the patient (who had over twenty years' Indian experience) agreed to use the ipecac treat-

ment for a short time before operating on the liver abscess, the existence of which he did not doubt. Thirty grains of the drug were given daily from the 19th to the 27th, with the result that the temperature steadily fell, as shown in Chart 1, and the signs of acute hepatitis simultaneously subsided. On the 20th the pain over the liver and the sweating had both diminished and he slept better. By the 21st the pain had ceased over the liver, although it continued in a slight degree in the right shoulder for another day. On the 23d the temperature was normal and there was no pain or sweating, and all suspicion of liver abscess had disappeared. The patient was kept in the hospital up to the 22d of November, but had no more signs of dysentery or hepatitis and gained weight steadily. There was no shadow of doubt in the minds of all who watched this patient that the ipecac treatment averted suppuration in the liver.

DYSENTERY FOLLOWED BY HEPATITIS WITH TEMPORARY IMPROVEMENT, VERY ACUTE HEPATITIS TWO AND ONE-HALF MONTHS LATER SUCCESSFULLY TREATED WITH IPECAC.

CASE 2.—European, male, aged 26, admitted Aug. 20, 1907, with a history of dysentery eight months before, followed after three weeks by pain in the epigas-

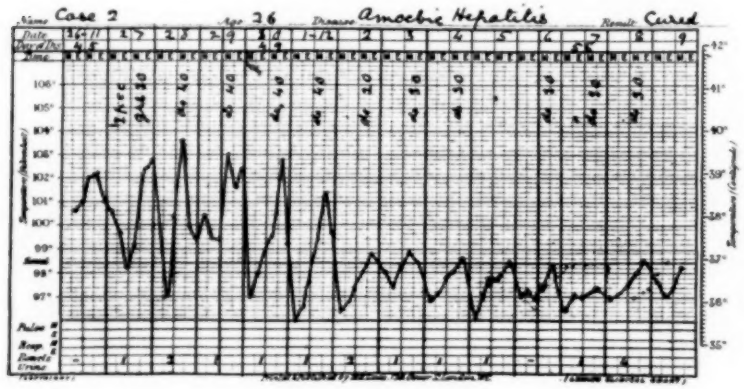

Chart 2—Case 2.

trium. On admission he had slight enlargement of the liver with pain over it. Stools loose, but no blood or mucus; intermittent fever rising to 101 or 102 F. in the evenings. The diaphragm moved well, and there was only slight increase of the leucocytes, with but 65 per cent. of polynuclears. The symptoms of hepatitis subsided in three weeks under salines and quinin, and he left the hospital apparently well. He returned two and a half months later (November 26), having had fever every evening for the previous month and a half, with rigor at times and sharp pain over the liver on and off. His bowels had been constipated. He was now weak and thin. There was slight bulging, without marked tenderness, in the hepatic region. The breath sounds at the right base were diminished, with a decrease of vocal fremitus and vocal resonance. The liver dulness extended from the fifth space to three inches below the costal margin in the nipple line. No edema was present, and the spleen was not enlarged. Under *x*-rays the right half of the diaphragm was found to be two inches higher than the left and scarcely moved even with deep respiration, but there was no shadow. A blood

count showed 3,570,000 red corpuscles, 15,000 white; ratio of white to red, 1 to 236; polynuclears, 77 per cent.; lymphocytes, 13 per cent.; large mononuclears, 9 per cent., and eosinophiles, 1 per cent. On account of the acuteness of the symptoms and the fulness in the hepatic region, liver abscess was suspected, but it was determined to try the ipecac treatment before operating, so 30 grains were given on the evening of the 27th and 40 grains on the following four evenings. On the 28th and 29th the hepatic pain was distinctly less, and the patient could turn over on his right side, which he could not do before. On the 30th there was no pain or tenderness over the liver. On December 2 his temperature remained normal for the first time, and a steady convalescence ensued, the liver receding until it was only just felt beneath the costal margin. The ipecac was continued in 30-grain doses at increasing intervals up to Jan. 5, 1908, in order to guard against the possibility of a relapse, and he left the hospital apparently quite well on January 5. The rapid lessening of the pain, followed by the decline of the fever and enlargement of the liver under the ipecac, was most striking in this case, and indicated that this treatment saved the patient from suppuration in the liver.

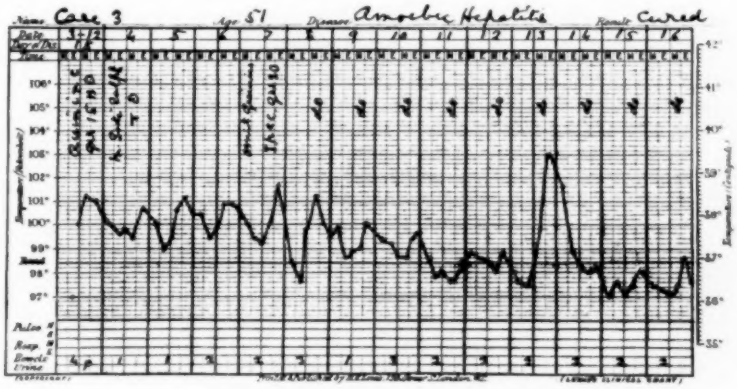

Chart 3—Case 3.

HEPATITIS WITHOUT HISTORY OR SYMPTOMS OF DYSENTERY RAPIDLY SUBSIDING UNDER THE IPECAC TREATMENT.

CASE 3.—European, male, aged 51, admitted on Dec. 3, 1907, for fever. He had been ill for two weeks with fever and pain in the right hypochondrium, with nausea and loss of appetite. No rigors, but feels chilly at times and sweats at night. Bowels constipated. The liver extends one inch below the costal margin and was very tender. Other organs normal. A blood count on the 11th showed 4,670,000 red corpuscles, 12,875 white; ratio of white to red, 1 to 363; polynuclears, 81 per cent.; lymphocytes, 12 per cent.; large mononuclears, 6, and eosinophiles, 1 per cent. Ipecacuanha was commenced on December 7, 30 grains being given each evening. Two days later the temperature began to fall and reached normal on the 11th, after which there was only one rise on the 13th, accompanied by a rigor, being possibly malarial in origin. On the 17th the liver had become reduced in size, being only just felt below the ribs, and the patient left the hospital apparently quite well on December 22 (Chart 3). This is an example of the less acute form of hepatitis, which drifts insidiously on into

suppuration after weeks of intermittent fever. It is only one step further to the class already mentioned, in which there is no pain or tenderness over the liver, and the presence of leucocytosis alone raises a suspicion of the true nature of the case, which is confirmed by the chronic fever yielding rapidly to large doses of ipecac.

METHODS OF GIVING IPECAC.

In giving large doses of ipecac in amebic dysentery and hepatitis, precautions have to be taken to avoid vomiting, especially if it is possible that an abscess of the liver has already formed. The usual method is to give either tincture of opium or chloral hydrate some twenty minutes before the freshly made pills or bolus of ipecac, no food or drink being given for several hours before and after the dose, which is best administered once a day in the evening. Recently I have had the drug put up in quantities of five grains in keratinised capsules, which are not dissolved until they reach the small intestines. This has worked very well, no antecedent sedative being required. Dr. F. B. Grubbs, of the United States Army, has recently informed me that the same desirable effect is obtained by coating ipecac pills with melted salol, but I have not yet had an opportunity of trying it. From 30 to 60 grain doses of the drug have been used, but the smaller quantity appears to be efficient. It should be continued for at least two weeks at increasing intervals, as two of my earlier cases, in which the ipecac was discontinued as soon as the temperature fell, relapsed some months later, presumably owing to the latent amebic ulcers not having been completely cured.

DURATION OF THE PRESUPPURATIVE STAGE OF AMEBIC HEPATITIS.

There remains to be considered a very important question: What is the usual duration of the presuppurative stage of amebic hepatitis, during which the ipecac treatment will avert the formation of an abscess of the liver? An examination of my records of the last seven years has furnished the following data on this point: Out of 53 native patients admitted to the hospital with liver abscess, often bulging through the thoracic or abdominal wall, 51 per cent. gave a history of over two months' illness, and 38 per cent. more between one and two months; 9 per cent. from two weeks to a month, and only one case, or 2 per cent., had been suffering for less than two weeks. Among 26 cases in Europeans there had been fever of hepatitis for over one month in 50 per cent., for from two weeks to a month in 34.6 per cent., and of less than two weeks in only 15.4 per cent, the times being 9, 9, 11 and 13 days, respectively, in these four cases. It is clear from these figures that in the vast majority of instances there is ample time for the diagnosis by blood examinations, etc., and for the ipecac treatment being carried out

during the presuppurative stage of acute amebic hepatitis. Very rarely multiple abscesses may develop within a few days with extreme acuteness, but even here the only chance of saving the patient is in the immediate ipecac treatment.

My experience of this treatment leads me to believe that it is not too much to say that over 90 per cent. of amebic abscesses of the liver can and ought to be prevented by the methods described in this and in previous communications, and thus one of the greatest scourges of some tropical countries may be conquered by the prompt use of a simple medicinal treatment, based on the correct conception of the true pathology of the disease derived from prolonged combined microscopic and clinical observation.

SNAKE POISONING IN THE UNITED STATES:

A STUDY BASED ON AN ANALYSIS OF 740 CASES.

PRENTISS WILLSON, M.D.
WASHINGTON, D. C.

General introduction.

PART 1.—The poisonous snakes of the United States.

Classification, number, distribution, habits and identification of the various species.

Anatomy and physiology of the poison apparatus.

PART 2.—Snakebite in the United States: frequency, pathology, symptoms, complications and sequelæ, duration, cause of death, diagnosis, prognosis and treatment.

General summary and conclusion.

Knowledge concerning snake poisoning in the United States is decidedly meager. The infrequency of the occurrence and the mildness of the symptoms in so many of the cases, do not encompass the subject with a degree of practical importance sufficient to stimulate much interest in it; hence the articles in the text-books are incomplete, in some instances contain serious misstatements, and uniformly convey to the casual reader totally erroneous impressions. The obviously important subject of the geographical distribution of the different venomous species has been practically ignored. The mortality and prognosis have remained largely matters of conjecture. Small effort has been made to bring the recommendations for treatment up abreast of the recent advances in our knowledge of the toxic properties of venoms. For these reasons the present paper has been undertaken. I have aimed at making the consideration a practical one, but have not hesitated to draw fully on the voluminous literature of the experimental side of the subject.

PART 1.—THE POISONOUS SNAKES OF THE UNITED STATES.

In the animal kingdom, one of the orders under the class *Reptilia*, is *Ophidia*, which includes all the true snakes. The *Ophidia* are divided into two sub-orders, *Ophidia colubridæ* and *Ophidia viperidæ*, or colubrine and viperine snakes respectively. The colubrine snakes are largely absolutely harmless, although the venomous species belonging in this sub-order are among the most deadly known. Fortunately the list of colubrine species in the United States includes only two which are sufficiently venomous to be dangerous to man. These are the coral snakes which will be described in detail later. The viperine snakes are divided

into two families, the *Viperinæ*, or true vipers, and the *Crotalinæ*, or pit-vipers, all the species in both families being venomous. The true vipers are confined entirely to the old world. The pit vipers are more universal in their distribution, but the greater number is found in the Western Hemisphere. With the exception of the two venomous colubrine species, the coral snakes, all the poisonous snakes found in the United States belong to this family.

THE CROTALINE SNAKES OR PIT VIPERS.

The pit vipers have been so named because of the presence of a pit or fossa on the side of the face below and between the nostril and the eye. The various species found in the United States belonging to this family represent three genera, *Crotalus*, *Sistrurus* and *Ancistrodon*. Of these the first two are all rattlesnakes while the last is represented by but two species, the copperhead, *Ancistrodon contortrix*, and the water moccasin, *Ancistrodon piscivorus*.

Thirteen species of rattlesnakes, and three or four varieties sometimes placed as distinct species, are found within the limits of the United States. Formidable as this statement appears it is in reality far from being so, as will be seen when the distribution of these species is studied. These snakes, so named from the termination of the tail in the rattle, a structure too well known to require description, are placed in two genera, the distinction being made because of a different arrangement of the scales and plates covering the dorsal surface of the head.

Sistrurus.—In the genus *Sistrurus* the integument covering the head is arranged in a series of large plates, in a manner similar to that found in the harmless snakes and in all the venomous species save rattlesnakes of the genus *Crotalus*. The two distinct species included in the genus are the ground rattler, or pigmy rattlesnake, *Sistrurus miliarius* and the massagua, *Sistrurus catenatus*. The little ground rattler rarely exceeds eighteen inches in length. It is found only in the South, from North Carolina, along the Gulf into Texas, and for some distance up the southern tributaries of the Mississippi. The massagua is larger than the preceding species, adult specimens measuring between two and three feet. It ranges from well into Canada through western New York, Michigan, Ohio, Indiana, Wisconsin, Minnesota, Iowa, Illinois, Nebraska and Kansas, being rare and in places exterminated in many parts of the range mentioned. In Texas and the Southwest it is replaced by a variety of the typical species, *S. catenatus Edwardsii*.

Crotalus.—The species of rattlesnakes belonging to the genus *Crotalus* are eleven in number in the United States. All of these are char-

acterized by having the head covered dorsally with scales quite like those found on other portions of the body, the large plates being fewer in number and differing in arrangement from those in the genus *Sistrurus*. The distinction between these two genera of rattlesnakes has a practical interest for the physician, the two species belonging to *Sistrurus* being much less dangerous than those of *Crotalus*. Of the eleven species of the latter genus, only a few need be mentioned specifically. The diamond-back rattler, *Crotalus adamanteus,* the largest of our venomous species, attains a length of over eight feet. It is distributed through Georgia, Florida and the Gulf States to the Mississippi. In Texas it is replaced by a slightly smaller species, *C. atrox*. In the North, this genus is represented by three species: In the East, extending from New England to Florida and westward to Texas, Iowa and Kansas is found the banded or timber rattlesnake, *C. horridus*. This specie aver-

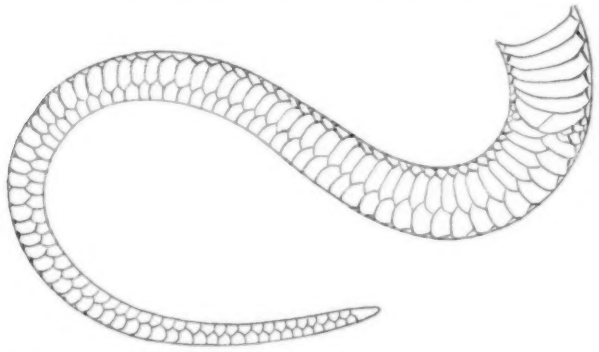

Fig. 1.—Underside of tail of water snake, *natrix* (after Stejneger).

ages from three to four feet in length for adult specimens, and rarely, if ever, exceeds six feet in length. In the states of the Middle West, from Canada to Texas, the prairie rattlesnake, *C. confluentus,* is found. Its average length is a little over three feet. West of the Rocky Mountains, from British Columbia to Southern California, the Pacific rattlesnake, *C. oregonus (C. lucifer),* is the only rattlesnake found. The six species of the genus *Crotalus* which have not been specifically mentioned are confined to the territory extending from the Mississippi through Texas, Arizona, Nevada, New Mexico, Utah and Southern California. Of these several are very rare and extend only a slight distance north of the Mexican boundary.

Ancistrodon.—The copperhead and the southern water moccasin are the only two species representing the genus *Ancistrodon* in the United

States. The copperhead, *A. contortrix*, is also known in different portions of its range as the red adder, chunkhead snake, pilot snake, upland moccasin, spreadhead snake, or moccasin. It is essentially an eastern species, extending as far west as Kansas, Oklahoma and Texas. Its northern limit is probably central Massachusetts, although it has been described from Vermont. In the South it is common, except in the peninsular portion of Florida, where it seems to be entirely absent. Michigan, Wisconsin, Nebraska and probably Iowa are free from this reptile. This is not a large species, adult specimens seldom, if ever, exceeding three feet in length, most specimens being considerably shorter. It frequents rocky hillsides bordering water courses, sometimes fields and woods, and is particularly likely to conceal itself under loose planking and rocks around barns and other out buildings. The general color is brown. Dorsally, the ground color is a bright hazel brown, which is very bright and distinct on the head. On either side of the body there are from fifteen to twenty-six dark chestnut colored irregu-

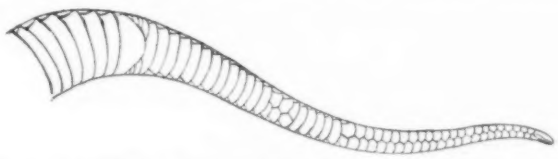

Fig. 2.—Underside of tail of water moccasin (after Stejneger).

larly triangular blotches, the base of the triangles resting on the ventral scales, the apices being in the median line dorsally. Ventrally the general color is a dull yellow, irregularly marked with dark blotches.

A snake frequently mistaken for the copperhead is the hog-nosed snake, *Heterodon platyrhinus*. This absolutely harmless species is mentioned here because, as stated, it is so often confused with the copperhead, and because even when properly identified it is almost always stated to be venomous. The dread in which it is popularly held is shown by the common names given it, such as sand viper, spreading adder and blowing adder. This snake is readily distinguished from the copperhead by the absence of those features to be described later, which render the recognition of the venomous species so easy, and in addition, by its turned-up snout, different coloring, and characteristic habits. Being fond of basking in open sandy spots, where rapid escape is impossible, the hog-nosed snake has evolved for its protection the ingenious habit of making itself look even more terrifying than the really dangerous species. In the presence of danger, it flattens

the head, expands the anterior portion of the body, and blowing and hissing strikes right and left at the object of its dread. If handled roughly it sometimes bites, but as I know from experience the wounds inflicted are merely a few tiny superficial abrasions with absolutely no after effect.

The water moccasin, *Ancistrodon piscivorus*, sometimes called the cotton-mouth or branch moccasin, is a southern species. It is fairly common in different localities in North Carolina and becomes more frequent in the states farther south, being most common in all the Gulf states as far as the Mexican boundary. It ascends the Mississippi into Missouri, southern Illinois, and western Kentucky, and is reported up

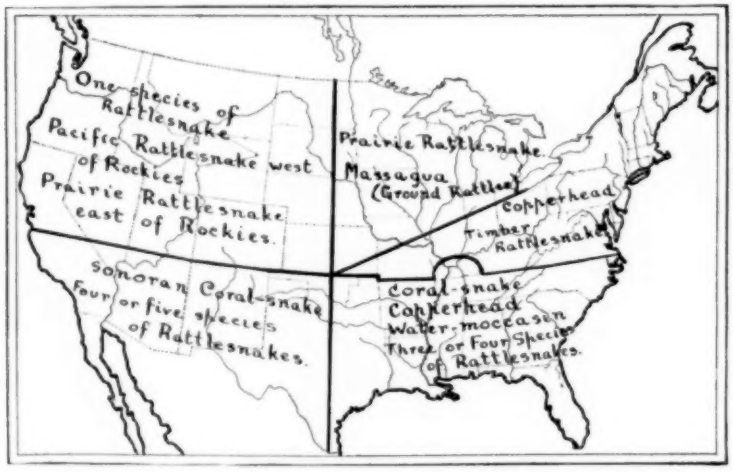

Fig. 3.—Distribution of the Poisonous Snakes in the United States.

the Ohio river as far as the Wabash. By way of the Arkansas river it invades the state of the same name, probably extending into Oklahoma. In eastern Texas it ascends the rivers as far as Dallas, and is very common in all that part of the state bordering on the Gulf. The water moccasin is semiaquatic in its habits and is seldom found far from water. It prefers to bask in the hot sun, stretched out on half submerged rocks and logs, and also climbs into the branches of the low bushes overhanging water. The rice fields of Louisiana fulfill all the conditions required by this species, and in them it is very common and greatly feared by the negro laborers. This snake is larger in every way than the copperhead, and some specimens exceed four feet in length. Its

general color is a very dark blackish brown, frequently so obscured by the dried mud clinging to it as to be scarcely recognizable. Its head is a dark purplish black in color and the body is marked on either side by from twenty to thirty narrow bars of the same color. Ventrally the animal is black, mottled with blotches of a dirty white.

The evil reputation of this reptile has spread far beyond the area infested by it, and as a result all water snakes are held in ill repute. As a matter of fact the reverse is the case, the water moccasin being the only venomous species showing any fondness for the water. Several water snakes are confused with the dangerous species, as is shown by the popular names bestowed upon them, such as copper-bellied moccasin and banded water moccasin. These are all varieties of the harmless water snake, *Tropidonotus fasciatus*. A large southern species, occurring coincidently with *A. piscivorus*, is *Tropidonotus toxipilotus;* although a dangerous looking reptile it is perfectly innocuous. All these harmless species may be differentiated from the true water moccasin, by the difference in color and the absence of the characteristic features of the pit vipers to be detailed later. In addition it may be stated that *T. fasciatus* and its varieties are distributed over a wide area in which the venomous species is never found.

THE VENOMOUS COLUBRINE SPECIES.

Of all the colubrine snakes in the United States, the two species sufficiently venomous to be dangerous to man are the coral snake or harlequin snake, *Elaps fulvius*, and the Sonoran coral snake, *Elaps euryxanthus*. These two species are so closely related and so similar in every way as to make their distinction of no practical importance to the physician. Both are confined in their distribution to the southern states. The range of *Elaps fulvius* is similar to that given for the water moccasin. It is found from North Carolina throughout the Gulf states to western Texas and ascends the Mississippi as far as southern Ohio. *Elaps euryxanthus* is a western species the range of which has not yet been definitely settled. It is known to be confined to the states of the Southwest and seems to be most numerous in Arizona. These two very interesting and very dangerous reptiles are fortunately rarely encountered by man. They are retiring in disposition, and spend most of their time burrowing under ground or hidden under the bark of old logs or in the dead leaves. The body is slender, rarely over three feet in length, and the head is small and only slightly differentiated from the neck. The color pattern is a most striking one, consisting of alternate broad rings of red and black, completely encircling the body, and

separated by narrow rings of yellow. On the tail the red rings disappear, the color being alternately black and yellow.

The general appearance of the coral snakes is more or less closely simulated by several harmless species, particularly by the different varieties of the milk snake, *Ophibolus doliatus*. The distinction may be made by remembering the distribution and habits of the coral snakes, and also that in them the colored rings extend across the ventral surface of the body, while in the harmless species the abdomen is white or blotched, and shows no trace of the rings. In the venomous species the black rings are bordered with yellow, the reverse being true in non-venomous snakes.

An interesting group of colubrine snakes, the *Opistoglyphs*, is of much more importance to the herpetologist than to the physician. They are mentioned here for the sake of completeness, and because they contribute toward swelling the total number of venomous species, stated by text-books to be found in the United States. The *Opistoglyphs* are characterized by the possession in the posterior portion of the upper jaw of a series of grooved fangs, intended for the injection of venom. These structures place them undeniably among the poisonous colubrines, but the position of the fangs in the back of the mouth, and the small size of the species found in the United States renders it very doubtful if the bite of these reptiles would be more than the most trivial affair. So far as as I know, not a single case of bite by any of these species has been reported. Brief notes on the species found in the United States are appended: The Jews-harp snake, *Trimorphodon lyrophanes*, and the annulated snake, *Sibon septentrionalis*, reach a length of from two to three feet. Both are confined to the states of the extreme southwest and are the only species which may be considered as possibly capable of inflicting poisoned wounds in man. The black banded snake, *Erythrolamprus imperialis*, found in southern Texas, attains a length of about one foot. Four species of *Tantilla*, one in the southeast and three in the southwest are absolutely innocuous for man, being hardly larger than large earth worms.

THE IDENTIFICATION OF THE POISONOUS SNAKES.

An ability to differentiate correctly between the harmless and venomous snakes may frequently be of the greatest importance. In the preceding descriptions of the various venomous species, mention has been made of the harmless snakes most likely to be confused with them. Here it is intended to point out those general features possessed by all the poisonous snakes, which fortunately are sufficiently characteristic

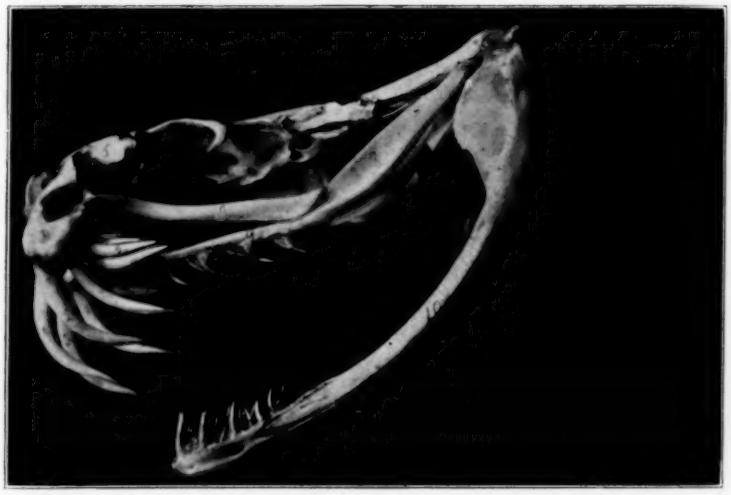

Fig. 4.—Lateral view of Skull of *Crotalus horridus* (from a photograph). 1. Active fangs. 2. Reserve fangs. 3. Upper maxillary. 4. Fossa for lodgment of the pit. 5. Lachrymal. 6. Frontal. 7. External pterygoid. 8. Quadrate. 9. Internal pterygoid. 10. Lower jaw.

to make their identification comparatively easy. The great structural differences between the viperine and colubrine species, make it necessary to consider the two separately.

All the pit vipers, rattlesnakes, copperhead, and water moccasin, correspond very closely with the popular ideas concerning the general appearance of the poisonous snakes. The head is broad and triangular and sharply differentiated from the neck. The body is thick and heavy in comparison with its length, and the tail short and blunt. The general sinister appearance of these reptiles is of little or no practical significance, however, since it is very closely simulated by many of the absolutely harmless species. The three features characteristic of all the pit vipers and of no other American species, the detection of any one of which establishes beyond all doubt the venomous nature of any given snake, are first, the presence in the anterior portion of the upper jaw of two hollow erectile fangs; second, the pit; and third, the presence on the ventral surface of the tail of scales undivided in the median line.

The fangs, as a very essential part of the poison apparatus, will receive detailed consideration later. It should be mentioned here, however, that in dead specimens they will be found folded against the roof of the mouth, very much as the blade of a pocket knife folds against the handle, and in this position are so covered by folds of the mucous membrane as readily to escape detection. By scraping the upper jaw from behind forward with some sharp object they may be brought into view. In addition to the fangs there is on either side of the upper jaw a single row of fine retrocurved teeth, while in the harmless species there is a double row on either side, the fangs being, of course, absent.

The pit, the structure from which the whole family receives its name; is a deep depression, lined by an epithelial membrane, which is lodged in a fossa on the outer aspect of the superior maxillary. It is seen in Figures 5, 17, and the fossa in the maxillary bone in Figure 4, 4. The rich supply of nerve fibers to the epithelial lining of the pit, renders it probable that the function of this peculiar structure is to act as an accessory sense organ. Although its exact function in the snake's economy is unknown, there can be no doubt that it serves as a most useful and unfailing means of recognizing the members of this dangerous family, and its absence in any specimen under examination, obtained in the United States, establishes its harmless nature, with the single exception of the coral snakes.

In Figures 1 and 2 is well illustrated a striking difference between the pit vipers and all the colubrine snakes, both harmless and venomous. In all snakes the ventral surface of the body as far back as the vent is

covered by overlapping scales, extending undividedly from one side of the body to the other. In the pit vipers many of these scales on the ventral surface of the tail, from the vent to the tip, retain this arrangement, extending unbrokenly across the body, while in the harmless species and also in the coral snakes, from the vent to the tip of the tail all the scales are divided in the median line. It is obvious, however, that it is not necessary to examine for this important point if the species of pit viper happens to be a rattlesnake. Here the presence of the rattle settles the venomous nature of the reptile at once.

In addition to the three important differential points which have been given consideration it may be mentioned that the pit vipers are ovo-viviparous, retaining the egg until the escape of the embryo. Some harmless species reproduce in the same way. The number of young produced by the pit vipers at one birth is comparatively small, many wild stories to the contrary notwithstanding. In the crotaline snakes, also, the pupil of the eye is vertical and cat-like, instead of round as in the colubrines. (Fig. 6, 19).

In identifying the coral snakes, the main dependence must be placed on the presence of the fangs, and on their peculiar and gaudy coloring, which has been described. In these reptiles the absence of the pit and the presence of divided scales on the ventral surface of the tail makes their positive recognition more difficult. The fangs of the coral snakes, as in the pit vipers, are situated in the anterior portion of the upper jaw, but differ from them in their comparatively and absolutely smaller size, and in being permanently erect. These differences will be explained more in detail later on. On either side of the upper jaw these snakes have but one row of teeth, the harmless species, as has been stated, having two.

GENERAL DISTRIBUTION OF VENOMOUS SNAKES IN THE UNITED STATES.

In Figure 3, the attempt has been made to indicate the number of venomous species in different portions of the country, rather than the exact limits of the range of the various species, which point has been given consideration above. It will be seen that in the greater portion of the North, one, and at most two species of rattlesnakes are all that are found in one locality, and that the only other venomous species present here is the copperhead, confined entirely to the East. In the South, the eastern states and Texas harbor three or four species of rattlesnakes, also the copperhead, water moccasin and coral snake; the western states having only the Sonoran coral snake in addition to several species of rattlers.

The reader is now in a position to pass judgment on the statement found in several text-books, that twenty-seven species of poisonous snakes are found in the United States. This figure, probably arrived at by counting up the number of species described by Stejneger,[1] includes seven species of opistoglyphs of no importance to the physician, and three species of rattlesnakes considered by many to be mere varieties. Eliminating these, the number remains at seventeen. To so state without proper qualifications, however, is to give impressions only a little less erroneous than those given by the larger number. Stejneger's work was written from the view point of the scientific herpetologist. From the point of view of the physician, it may be stated that the venomous snakes of the United States are the rattlesnakes, several species being described, the copperhead, the water moccasin and the coral snake.

ANATOMY AND PHYSIOLOGY OF THE POISON APPARATUS.

While an exhaustive account of the anatomy and physiology of the mechanism by means of which the poisonous snakes elaborate and inject their venom would obviously be out of place in this paper, a certain amount of knowledge on this subject is necessary to a comprehension of many points of practical importance in the consideration of snake poisoning. Such readers as may have a special interest in the subject are referred to Mitchell's[2] original account, or that given by Stejneger.[1] The poison apparatus will first be described as it exists in the pit vipers and then the differences existing in these structures in the coral snakes will be pointed out.

In Figure 4, a lateral view of a skull of *Crotalus horridus* is presented. It will be seen that the upper maxillary bone is greatly shortened from before backward. Externally it presents the fossa for the lodgment of the epithelial pit, and posteriorly articulates with the elongated external pterygoid. Above it articulates by means of a ginglymus joint with the lachrymal bone, which in turn articulates with the frontal. Below it bears the single perforated poison fang, firmly fixed in its socket and not in itself movable, as is often stated. Behind the active fangs are seen the reserve fangs, ready to be pushed forward to replace the active fang in case of its loss by accident or shedding. In the recent state these reserve fangs are completely hidden and surrounded by the mucous membrane. The fang itself is a hollow, curved tooth, the convexity of the curve being directed forward, containing two

1. Stejneger, L.: The Poisonous Snakes of the United States, Rep. U. S. Nat. Mus., 1893, Washington, 1895, pp. 337-487.

2. Mitchell, S. W.: Researches on the Venom of the Rattlesnake, Smithsonian Contrib. to Knowl., 1860, xii.

canals, an anterior and a posterior; of these the former is the canal for the venom, the latter the dental canal. The canal for the poison runs along the anterior convex border of the fang, from an upper aperture near the base of the tooth anteriorly, to the lower slit-like opening on the convex border near the point. The poison canal is lined by the same enamel as that covering the surface of the fang, showing the method of its formation, namely, an infolding of the anterior surface of the tooth. As has been stated, the normal position of the fang in the quiescent condition of the snake is folded back against the roof of the mouth, as is shown in Figures 5 and 6. In this position absolutely useless as a weapon, the fang is brought into a position of erection suitable for its use, by muscular action on the bony mechanism described. The muscle concerned is the sphenopterygoid, unfortunately not shown in any of the illustrations, which takes its origin from the median basal ridge of the skull, anteriorly, and passes backward and outward to be inserted into the inner aspect of the quadrate bone, seen at Figure 4, 8. It will readily be seen that the result of the contraction of this muscle will be to draw the quadrate forward, which motion will be imparted to the external pterygoid causing it in turn to act on the superior maxillary. As a result of the force so applied, and in virtue of its articulation with the lachrymal, the superior maxillary rotates downward and forward causing the fang to sweep through the segment of a circle until it comes into a position almost at right angles to the line of the upper jaw and most favorable for its use as a weapon of defense. In Figure 4 the fangs are shown in a position of almost complete erection.

The poison gland is an almond-shaped body lying below and behind the eye, extending backward to a point about on a line with the commissure of the lips. Its size varies with the size of the snake; a gland from a rattlesnake four feet long measuring eight-tenths of an inch in length (Mitchell). The gland is held in position by prolongations of its outer facial covering, the most important being the internal or suspensory ligament and the posterior ligament, running backward to the articulation of the lower jaw. Running through the center of the gland is a single slightly dilated duct, which receives the contents of the smaller ducts from the secreting acini. In this central duct and its prolongation from the gland to the base of the fang the venom is stored ready for use. The course of the duct is forward from the gland to the maxillary bone around which it winds to terminate in a manner to be described close to the upper aperture of the poison canal in the fang. Immediately under the eye, it presents a sharp curve and at the same point a noticeable enlargement due to the presence there of a band of muscular tissue

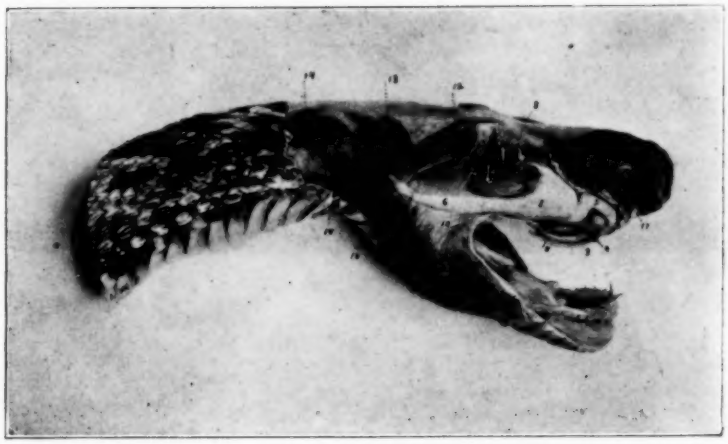

Fig. 5.—Superficial dissection of the poison apparatus of *Crotalus adamanteus* (from a photograph). 1. Poison gland. 2. Poison duct. 3. Fang. 4. Inner fang sheath. 5. Cut edges of outer fang sheath. 6. Posterior ligament of gland. 7. Anterior temporal muscle. 8. Middle temporal. 9. Posterior temporal. 10. Facial insertion of fibers of the middle temporal. 11. Mandibular portions of the anterior and posterior temporals. 12. Digastric. 13. Cervico-angular. 14. Cervico-mandibular. 15. Costo-mandibular. 16. External pterygoid. 17. Pit.

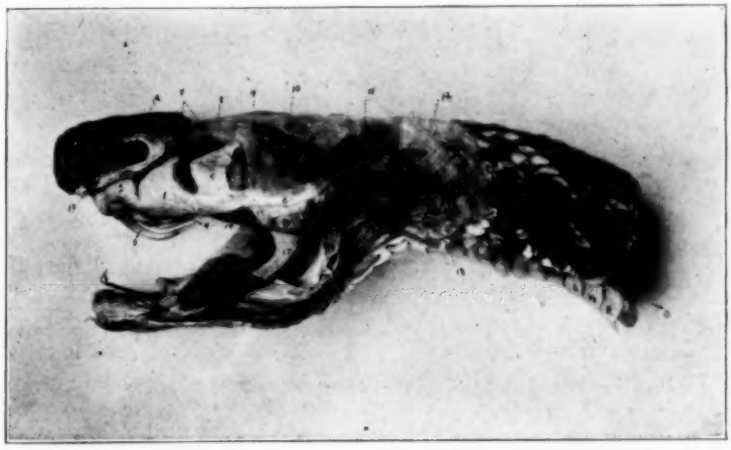

Fig. 6.—Deeper dissection of the poison apparatus of *Crotalus adamanteus* (from a photograph). 1. Poison gland. 2. Duct. 3. Fang. 4. Sheath of opposite fang. 5. Internal or suspensory ligament of gland. 6. Posterior ligament of gland. 7. Cut edges of anterior temporal muscle, showing the sharp down curving around the posterior border of the gland. 8. Middle temporal. 9. Posterior temporal. 10. Digastric. 11. Cervico-angular. 12. Cervico-mandibular. 13. Costo-mandibular. 14. External pterygoid. 15. Mandibular portion of anterior and posterior temporals. 17. Lower jaw. 18. Pit. 19. Vertical pupil.

constituting a true sphincter, first described by Mitchell.[2] The capacity of the duct from its cecal extremity in the gland to the sphincter varies, of course, with the size of the snake. Usually its capacity is but a few drops, and only in very large specimens does it exceed fifteen or twenty drops.

The relation of the poison gland to the two muscles now to be described is of the utmost importance. The anterior temporal muscle in the pit vipers has completely lost its attachment to the temporal fossa and takes origin entirely from the fascia covering the gland on its upper surface. From this origin the muscular fibers pass at first backward and then downward around the posterior border of the gland, passing between the suspensory and posterior ligaments of the same, and continuing downward find their attachment on the lower jaw. It will be readily seen that the contraction of this muscle will, in addition to closing the lower jaw, forcibly compress the upper and posterior portions of the gland. The external pterygoid muscle takes its origin from the posterior aspect of the articulation of the lower jaw. From this point it passes downward for a short distance and then turning sharply forward passes under the articulation internal to the ramus of the jaw and external to the quadrate bone and runs forward to a point directly under the poison gland, with which it is in the closest relation. The fibers of this muscle have the following three insertions: a portion, becoming aponeurotic, spreads out on and blends with the facial covering of the gland below and anteriorly. Another portion, becoming tendinous, is inserted into a tubercle on the posterior aspect of the upper maxillary bone just below its articulation with the external pterygoid. The third portion is lost in the sheath of mucous membrane investing the fang. When contracting, then, this muscle depresses the fangs by drawing the superior maxillary bone directly backward, thus proving itself the direct antagonist of the sphenopterygoid, which, as has been stated, causes its erection; presses on the lower and anterior portions of the poison gland; and finally, has an action on the sheath of the fang, yet to be described. It will thus be seen that the anterior temporal and external pterygoid muscles acting together subject the whole of the poison gland to a very considerable degree of pressure, calculated, if associated with the relaxation of the sphincter of the duct, to completely milk the gland and duct of their contents.

There now remains to be described the arrangement by means of which the venom expelled from the duct finds its way into the poison canal of the fang. As the fang lies in its quiescent condition against the roof of the mouth it is completely hidden from view by a tubular

sheath of mucous membrane. In Figure 5, this sheath is seen split open, its cut edges showing at 5 and the fang at 3. Toward the base of the fang this sheath seems to present an inner gum-like process, seen at 4, of firmer consistency than the rest of the sheath, closely clasping the fang just below the upper aperture of the poison canal. Into the cup-like cavity formed by the inner sheath, or gum, the opening of the duct from the gland is found. It will be seen, therefore, that there is no direct communication between the duct and the poison canal, the venom escaping from the former into the cavity of the gum-like structure around the base of the fang, and from thence taking the course along the path of least resistance through the only opening presenting itself, the upper aperture of the poison canal. When the fang is erected its membranous sheath becomes crowded back around the base, probably aiding by its pressure, in more closely approximating its inner portion to the base of the fang. Judging from the considerable number of muscular fibers passing into this sheath from the external pterygoid muscle, as has been described, there is reason to think that this approximation is decidedly an active, as well as a passive process.

In making use of the diabolically ingenious mechanism which has been described, the pit vipers have first to imbed the fangs in their victims and then to eject their supply of venom. In accomplishing the first of these objects, the reptile prefers to strike from a coil, although capable of inflicting its dangerous wounds from a great variety of positions. When angered or alarmed, the body is rapidly thrown into a series of circular coils, with the neck and upper portion of the body held loosely across the coiled mass in a succession of S-shaped curves. In the rattlesnakes the tail is held vertically, vibrating with wonderful rapidity, causing the well-known sound of the rattle. In launching itself forward to the attack the snake simply straightens out the S-shaped curves by contracting the muscles on their convexities. By this simple maneuver the head is shot forward with a speed which the eye can not follow. At the same time that the head is thrown forward, it is bent backward, the jaws opened to a surprising degree, and the fangs erected. The whole action is entirely comparable to a swift forward thrust with a double pointed dagger. Having thus imbedded its fangs the animal now proceeds with the injection of the venom; the various muscular acts described in this connection of course occur synchronously. With the fangs still imbedded in the tissues, they are drawn back and depressed, in order to deepen the wound, the lower jaw is forcibly closed on the part in a vicious bite, and the sphincter guarding the duct is relaxed. In performing these movements the anterior temporal and external pterygoid muscles are

brought into play, their contraction automatically compresses the whole of the gland and causes an ejection of venom from each fang into the tissues in which they are imbedded. Having accomplished its purpose the reptile disentangles itself from the wound and rapidly renews its coiled attitude prepared for further hostilities.

The essentials of the poison apparatus in the coral snakes are very similar to those in the pit vipers. On either side of the head there is a gland for the secretion of venom, connecting by means of a duct with a perforated fang, situated in the anterior[3] portion of the upper jaw. The fangs, however, are not depressible at the will of the snake, but maintain a permanently erect position, comparable to the canine teeth of the carnivora. They are both absolutely and relatively smaller than the fangs of the pit vipers of similar size. The mouth in these snakes is very small. For these reasons it is practically impossible for the coral snakes to inflict a wound except on the bare skin, and under exceptionally favorable conditions. In most of the few reported cases of bites of these species, the reptile has bitten while being carelessly handled. The action is a bite, pure and simple, the fangs being introduced with a chewing motion, and there is none of the striking seen in the pit vipers.

PART 2.—SNAKE-POISONING IN THE UNITED STATES.

The series of cases on which, in as large a measure as possible, this study is based, numbers 740 cases, of which 440 have been collected from the literature, and the remainder from various private sources. In both classes of cases, however, the clinical records have been so deficient, so lacking in the most essential details, that it has been found necessary to draw largely on the reports of the different investigators now working on venom intoxication along experimental lines. The section dealing with the toxicology of venom is intended only as a brief review of those phases of the present knowledge of this most interesting subject which have a direct and practical bearing on the matter under discussion. In regard to the frequency of occurrence of various symptoms and complications it has been considered inadvisable, and indeed impossible in most instances, to give exact figures, the number of full case reports being entirely too small to render such an attempt satisfactory. The figures given in the sections on mortality and prognosis, however, are based on a much larger number of cases than has before been available, and for reasons there presented are thought to be of considerable accuracy.

3. Noguchi's statement that the fangs in these species are situated in the posterior portion of the jaw, Osler's Modern Medicine, vol. i, page 248, is an error. See Stejneger, loc cit, page 356.

FREQUENCY.

The frequency of snake bite in the United States is largely problematical. In the older and more thickly settled portions of the country it is a rare occurrence. During the summer of 1907, however, two cases, due to the copperhead, occurred in the immediate vicinity of Washington, D. C. There can be no doubt that the poisonous snakes, especially the rattlesnakes, are being slowly but surely exterminated and as a result their bites are becoming more and more infrequent. Even in the South and Southwest, where the venomous species are most common, bites seem to be matters of rather rare occurrence. Many physicians practicing in these localities see but one or two cases in years of practice. Many cases, however, especially those due to the smaller rattlers and the copperhead, are never seen by physicians, the laity being well aware of the uniformly good prognosis of such cases. It is interesting to note that not a single case of snake bite is reported in the Medical and Surgical History of the War of the Rebellion, and that the condition does not seem to figure at all in the vital statistics of any of the states[4]. Everything considered my opinion would be that the total number of cases occurring annually is probably less than five hundred, possibly considerably less.

In regard to the relative frequency of bites by the different species more definite statements can be made. In 566 cases in the series in which the species of snake causing the injury was known, there were 408 cases of rattlesnake bite, 97 cases of copperhead bite, 53 cases of water moccasin bite and 8 cases of coral snake bite, representing respectively 72 per cent., 17.1 per cent., 9.3 per cent. and 1.4 per cent. of the series. The predominance of rattlesnake cases is only natural when the number of species and wide distribution of these snakes is considered. On the other hand, the figure of 17.1 per cent. for copperhead cases is probably too low. This snake is widely distributed in the eastern portion of the country and in many localities is the only venomous snake found. Its bite, however, is usually not a serious affair, and comparatively few cases receive medical attention. The habits of the water moccasin and its limited distribution accounts for the infrequency of bites by this species. As might be expected from the retiring habits of the coral snakes and the very small size of the mouth, bites by these snakes can only occur under most exceptional circumstances, as when the reptile is being carelessly handled, and the rate of 1.4 per cent. is entirely too high.

4. With the exception of Florida: the vital statistics for the years 1892 to 1899 give snake bite as the cause of death in thirteen cases.

PHYSICAL, CHEMICAL AND TOXIC PROPERTIES OF VENOM.

Venom is a viscid, greenish or yellowish fluid, usually clear, of acid reaction, and with a specific gravity ranging between 1035 and 1065. When dried it assumes the scaly, cracked appearance of dried egg albumen, and in this form retains its toxic properties almost indefinitely. In the process of drying there is a loss of from 25 per cent. to 50 per cent. in weight. Chemically, our knowledge of venom is far from perfect, and the exact classification of the various proteid constituents is still largely undecided. For the present purpose, however, any exhaustive discussion of this phase of the subject is unnecessary. It need only be said that, as first pointed out by two Americans, Mitchell and Reichert,[5] venom is a toxin of wonderfully complex activity, a complexity depending on the presence of a varying number of different toxic principles. Since the epoch-making experiments of these authors, serpent venoms have been investigated in laboratories all over the world, and the literature of the subject has reached voluminous proportions. The result of all this study has been to show conclusively that in venom we have one of the most complex poisons known. Those particularly interested are referred to the recent summaries of the subject, in French, by Calmette,[6] and in English by Martin and Lamb.[7] According to the latter of these authorities the following toxic principles have been found in the different venoms studied:

1. A powerful fibrin ferment.
2. An anti-fibrin ferment.
3. A proteolytic ferment.
4. Various cytolysins, capable of acting on red blood cells, leucocytes, endothelial cells of blood vessels, nerve cells and the cells of various other tissues.
5. Agglutinins for red blood cells, etc.
6. An antibactericidal body of the nature of anticomplement.
7. A neurotoxin or neurotoxins with affinities for all nerve cells, and especially the cells of the respiratory center in the bulb.
8. A neurotoxin, with an affinity for nerve endings in muscles and for those in the diaphragm in particular.
9. A substance which causes greatly increased tone in cardiac

5. Mitchell and Reichert: Researches on the Venoms of Poisonous Serpents, Smithson. Contrib. to Knowl., 1886, xxvi.

6. Calmette, A.: Les venins et les animaux venimeux, Paris, Masson et Cie, 1907.

7. Martin and Lamb: Snake-poison and Snake-bite, in Allbutt's System of Medicine, 1907, vol. ii, part ii, 783-821.

muscle, and if in sufficient concentration, systolic standstill of the isolated heart.

Venoms obtained from different species vary in the relative proportion in which these various toxic elements are present and apparently, also, in their absolute toxicity, and on these factors depend the variations seen in the syndrome of poisoning by the different species. In a general way, venoms group themselves in two classes, the venoms in either class being characterized by a more or less similarity in their physiological action, corresponding, respectively, to their origin from the two great divisions of the venomous snakes, the *Colubridæ* and the *Viperidæ*.

The geographical limitation of the subject renders it unnecessary to devote much space to a detailed consideration of the colubrine venoms. As has been stated, the only venomous colubrine species of practical importance in the United States are the coral snakes. Fortunately, bites from these reptiles are excessively rare, but the symptoms noted in the few reported cases show conclusively that their venom is similar in its action to the general action of other colubrine venoms, and accordingly dangerous. These venoms are characterized by the severity of their attack on the central nervous system, by their peculiar selective action on the respiratory center, and by the comparatively mild local manifestations at the site of their innoculation. In some venoms of this class a curare-like action on motor nerve endings, particularly those of the phrenics in the diaphragm, has been observed. I know of no experimental investigation of the venoms of the coral snakes except a few isolated experiments reported by Mitchell and Reichert.[5] On the other hand a knowledge of the action of the viperine venoms is of the greatest importance to the American physician, since at least 99 per cent. of snake bites in the United States are caused by the pit vipers. A careful study of the venoms of the rattlesnakes, copperhead and water moccasin is therefore necessary. Practically all the work done on rattlesnake venom has been with venom obtained from *C. adamanteus* and *C. horridus*. These two species are in a large measure typical of the other and smaller species of the same genus, and of the species of the genus *Sistrurus*. It has been demonstrated clinically, as will be shown later, that the bites of the smaller rattlesnakes are less dangerous than bites of the large species mentioned, but this is probably due to a decreased dosage, rather than to material differences in the toxic composition of the venoms. In general, the action of all viperine venoms as compared with colubrine venoms is characterized by the severity of the local symptoms at the site of innoculation, by a much less vigorous attack on

the central nervous system, and a greatly diminished tendency toward a selective action on the respiratory center. Many venoms of the true vipers, and practically all pit viper venoms, also show a pronounced tendency toward the production of hemorrhages in various parts of the body.

The comparative toxicity of water moccasin, copperhead and rattlesnake venom for guinea-pigs has been found by Flexner and Noguchi[8] to be in the order named. Thus taking 0.1 mg. of cobra venom as the amount necessary to cause the death of a pig weighing 300 gms. in less than four hours, these authors found that it would require twice as much water moccasin venom, six times as much copperhead venom, and ten times as much rattlesnake venom, to cause the same results under similar conditions. Although it has been shown that the toxicity of different venoms varies for different species of animals, it seems reasonable to suppose that if the minimum lethal dose of water moccasin venom for guinea-pigs is one-fifth that of rattlesnake venom, the former must be more toxic for man than the latter. It must be emphasized in this connection, however, that the relative degree of toxicity of these venoms, even if it could be proven to hold true for man, is an entirely different matter from the relative degree of danger attending bites inflicted by these snakes. In determining the latter point, as will be shown later, the relative toxicity of the venoms is only one of several points which must be given careful consideration.

The greater toxicity of the *Ancistrodon* venoms is due to the presence in them of greater amounts of the neurotoxic principle, as first pointed out by Mitchell and Reichert[5] and confirmed by Flexner and Noguchi.[8] These experimental findings receive some confirmation from clinical observations to be given later, and in beginning the consideration of the neurotoxic action of the pit viper venoms it must be stated that the moccasin and copperhead venoms in their action approach more nearly the type of colubrine poisoning than does rattlesnake venom. The latter, however, does contain neurotoxin, as has been conclusively shown by Flexner and Noguchi,[8] who so treated rattlesnake venom as to destroy all its toxic properties save those for the nervous system, and then found that they were able to cause the death of experimental animals by injecting the altered venom in doses of from ten to twenty times the minimum lethal dose of the unaltered venom. In these cases the symptoms observed were entirely like those following the injection of typical colubrine venoms. These experiments would seem to show

8. Flexner and Noguchi: Univ. Penn. Med. Bull., 1901-02, xiv, 438, and 1903-04, xvi, 163.

conclusively that the neurotoxins play a comparatively unimportant part in causing death in cases of rattlesnake poisoning, provided, of course, that we consider the relative toxic powers of the neurotoxins of rattlesnake venom to be approximately the same for man and the animals used experimentally, rabbits and guinea-pigs. For in order to cause death by the neurotoxic action of this unaltered venom it would have to be injected in doses which would be overwhelmingly poisonous from the large amount of various other toxic principles present. There can be little doubt, however, that the depression of the functions of the cord following the injection of pit viper venoms, plays a not unimportant part in causing the general collapse characterizing these intoxications. This depressive action seems to have a tendency to affect the sensory side before the motor, and may be marked by complete loss of function resulting in more or less anesthesia and loss of motion. The respiratory center shares in the general depression, but is not selectively attacked by rattlesnake and only to a slight degree by moccasin and copperhead venoms. Any selective activity of the neurotoxins of these venoms seems to be directed against the vasomotor center.

On the circulation all the pit viper venoms have a most decided action, causing a profound fall in blood pressure which is often, undoubtedly, the cause of death. This action, clearly demonstrated by the experiments of Mitchell and Reichert[5] for both *Crotalus* and *Ancistrodon* venoms, has been recently studied by Rogers[9] with the venoms of the rattlesnake and several old world vipers. The findings of this author I considered of the greatest importance. He observed, following injections of rattlesnake venom, a decided fall in blood pressure, associated with dilation and congestion of the entire portal system and resulting in a complete failure of the circulation. To this condition of the circulation he attributed the failure of respiration, considering this to be a purely secondary phenomenon in cases of viperine poisoning. The circulatory failure is attributed to the depression of the vasomotor center in the medulla, a conclusion entertained many years previously by Mitchell and Reichert.[5] The therapeutic procedures recommended by Rogers in view of his experimental findings, will be considered later. It will thus be seen that one of the most important actions of the pit viper venoms is to profoundly lower blood pressure, in fatal cases to such a point that respiration fails because of lack of circulation in the already impaired respiratory center.

9. Rogers, L.: The Physiological Action and Antidotes of Colubrine and Viperine Snake Venoms, Phil. Tr. Royal Soc., London, 1901-1905, excvii, B., 123.

On the blood the venoms under consideration have several actions of the greatest importance; in producing or inhibiting coagulation, in causing hemolysis and agglutination, and in diminishing or destroying the bactericidal power of the blood serum.

The effect on coagulation is seen in both a positive and negative phase. Noguchi[10] is authority for the statement that the venom of *C. adamanteus* has the power to cause an immediate intravascular thrombosis, resulting in the speedy death of the subject. This intravascular thrombosis is rarely if ever the cause of death in actual cases of snake poisoning by American species, for in order to have this effect the venom would have to be received in large quantity immediately into the circulation, a combination of circumstances so excessively rare, as to be negligible. On the other hand, the negative phase, in which the clotting power of the blood is destroyed or seriously interfered with for a considerable length of time, is frequently observed clinically. It is doubtful, however, if this condition of the blood is of grave import, save in that it must predispose to the occurrence of hemorrhage.

The hemolytic and agglutinative properties of pit viper venoms are of greater theoretical than practical importance, and probably play a negligible part in actual cases of venom intoxication. Cytolysins and agglutinins for both red cells and leucocytes have been shown to be present in these venoms by Flexner and Noguchi.[8] Clinically the hemolytic action is shown by the frequent occurrence of hemoglobinuria. The relative power of these venoms to cause such blood changes is of interest as showing the difference in their toxic composition. Thus in causing hemolysis moccasin venom is fifty and copperhead venom twenty-five times as potent as rattlesnake venom, while in causing agglutination both moccasin and copperhead venom are twenty times as potent.

The great clinical importance of the changes induced in the bactericidal power of the blood serum by venom intoxication has not been sufficiently emphasized in the literature. Welch and Ewing[11] showed that in poisoned rabbits the blood serum had lost practically all its bactericidal properties, and to this condition they attributed the great rapidity of postmortem putrefaction. Flexner and Noguchi confirmed these findings with venoms of the rattlesnake, moccasin and copperhead. The relative potency of the venoms named in causing these changes does not seem to have been determined.

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10. Noguchi, H.: Snake Venoms, in Osler's Modern Medicine, i, 247-265.

11. Welch and Ewing: The Action of Rattlesnake Venom on the Bactericidal Power of the Blood Serum, Med. Rec., 1894, xlv, 663; also Lancet, 1894, i, 1236.

TABLE 1. FINDINGS IN FOUR AUTOPSIES FOLLOWING DEATH FROM RATTLESNAKE BITES.

Reporter.	Blood.	Brain and Cord.	Heart and Lungs.	Abdominal Viscera.	Local Findings.	Remarks.
1. Home[12]	Clots in heart.	Congestion of brain and its membranes, slight serous exudate.	Clots in heart. Half ounce of frothy fluid in pericardium. Lungs healthy.	Stomach congested, other viscera healthy.	Necrosis and sloughing of skin of arm. Finger had been amputated. Skin dissected up by offensive purulent serum. Some extravasation of blood in arm and on chest.	Death due to sepsis. Duration of illness 17 days.
2. Pihorell[13]	Fluid in cerebral sinuses and dura, coagulated in bitten arm.	Thickening of cerebral arachnoid and some adherence to dura.	Congestion of trachea and bronchi, which contained red, frothy mucus. Lungs healthy and crepitant, somewhat congested.	Healthy.	Very slight swelling around one bite. No changes in muscles.	Death after 9½ hrs. Surprisingly slight local manifestations.
3. Horner[14]	Entirely fluid, no coagulation.	Consistence of brain normal, but deep brown color due to congestion. No extravasation of blood. Cord normal. Membranes of both cord and brain injected. Serous exudate beneath cerebral arachnoid.	Hypertrophy of left ventricle. Heart empty.	A few ounces of serum in peritoneal cavity. Gastric mucosa intensely injected, but no ecchymosis. Numerous bright red inflammatory patches in small intestine, especially jejunum; walls infiltrated with serum; contents "dark bilious matter." Liver yellow and enlarged.	Local tumefaction due to serous infiltration.	Death after 18 hrs. Patient an alcoholic; condition of liver attributed to this cause. Contents of intestines may well have been altered blood.
4. Spaulding[15]	No clots found in heart.	Slight congestion and extravasation in brain and its membranes.	Pale and flabby, containing no clots. Lungs congested and edematous. One ounce of blood in each pleural cavity.	Stomach highly congested and partly filled with blood. Spleen and liver congested.	Considerable bloody extravasation in arm and right side as far down as groin.	Death after 28 hrs.

12. Home, Sir E.: Case of a Man Bitten by a Crotalus, Phil. Tr. Royal Soc., London, 1810, p. 75.
13. Pihorel: Observations sur la morsure d'un serpent à sonnettes, Jour. de physiol. expèr. et path., 1827, vii, 97.
14. Horner: Postmortem Examination of a Patient Who Died from the Bite of a Rattlesnake, Am. Jour. Med. Sc., 1855, xiii, 397.
15. Spalding: New York Med. Jour., 1884, xl, 66.

Among the cytolysins for the various parenchymatous cells, demonstrated to be present in all venoms, the most important in the pit viper venoms is undoubtedly the principle responsible for the multiple hemorrhages, the hemorrhagin of Flexner and Noguchi. These investigators have carefully studied the properties and mode of action of this substance. They say: "We look on hemorrhagin, therefore, in the light of a cytolysin for endothelial cells of blood vessels, the destruction of which is the direct cause of the escape of blood into the surrounding tissues." The actual giving way of the vessel wall and the escape of the blood has been observed under the microscope by many investigators. The most characteristic feature of crotaline poisoning, the decided tendency toward hemorrhage, is thus accounted for. The relative potency of different venoms in causing hemorrhages, which may depend on variations in the amount or quality of the hemorrhagin present, has been found by Flexner and Noguchi[8] to be as follows: If the cobra venom be taken as unity, then copperhead and moccasin venom are ten and rattlesnake venom one hundred times as potent. These figures show conclusively that the power to cause multiple hemorrhages is a common and decided characteristic of the pit viper venoms, since they are, in this respect, so much more powerful than the venom of the dreaded cobra.

Locally, in the subcutaneous and muscular tissues around the site of inoculation, the characteristically severe action of the crotaline venoms is due to many of the toxic principles already enumerated, the severity and extent of the lesions being caused by the concentration of the venom at this point. A proteolytic ferment is responsible for the softening and disintegration of the muscular tissues, and according to Noguchi[10] a principle analagous to hemorrhagin for the marked edema.

In summarizing the toxic action of the crotaline venoms, their ability to profoundly lower blood pressure, probably because of their direct selective action on the vasomotor center; their disintegrating action on the endothelium of blood vessels, resulting in the occurrence of multiple hemorrhages, and their antibactericidal effect on the blood serum, must be selected as their most dangerous properties. Their inhibition of coagulation, their functional depression of the whole cord and medulla, and the slight tendency exhibited by the two *Ancistrodon* venoms toward a selective action on the respiratory center, must be borne in mind.

PATHOLOGY.

Our knowledge of the macroscopic and microscopic lesions found after death from crotaline poisoning is limited and based almost entirely on experimental findings.

Certain gross pathologic changes have been found with great uniformity by various investigators, in the bodies of animals dying from venom intoxication. Locally, when the injection of venom has been subcutaneous, the muscles around the site of inoculation are found softened to the point of diffluence and dripping with extravasated blood. Evidences of antemortem pyogenic infection of the necrotic tissues are frequently observed. Petechial hemorrhages in the pericardium, endocardium, pleural cavities, peritoneum, mesentery, intestines, omentum, and even in the meninges, together with marked congestion of all the abdominal viscera, and less frequently of the lungs, are the lesions most frequently seen. The blood is generally found to be fluid and noncoagulable. Even in the small animals used experimentally antemortem, intravascular clotting is rare, except in cases in which the amount of venom injected was considerably in excess of the minimum lethal dose, and particularly when the injection was intravascular.

I have been able to find only four recorded autopsies in man, following death from the bites of American serpents, and of this number three have been previously commented on by Mitchell.[2] All are incomplete and would be worthless for the purpose of making any general deductions were it not for the similarity shown between the findings in actual and experimental cases of crotaline poisoning. The records of these necropsies are presented briefly in Table 1. Their great imperfection is evidenced at once by the single fact that the condition of the kidneys is not mentioned in a single instance. The first case, that of Home, is of little importance for showing the lesions of venom poisoning, death being undoubtedly due to secondary infection. It serves to emphasize, however, the destructive nature of the changes induced by septic infection of tissues previously devitalized by the activity of crotaline venoms. In the three remaining cases we are dealing with deaths due to the immediate toxic activity of the venom; the similarity of the lesions found, and their resemblance to those described in animal experiments, will be noticed. It seems worthy of mention that all the four rattlesnakes responsible for these deaths were in captivity and their bites were the results of careless handling.

Knowledge of the microscopic lesions in the various organs following venom intoxication is, so far as I know, dependent entirely on animal experiment. In those cases in which death has rapidly followed large doses of the venom the microscopic appearance of the parenchymatous cells has appeared to be little if at all altered. In more chronic cases of poisoning, however, especially where life has been prolonged for days, the cells of the various abdominal viscera show cytolytic changes; foci

of necrosis, often infiltrated with blood, make their appearance, degenerative changes in the myocardium are sometimes seen, and the kidneys may present the picture of acute hemorrhagic nephritis. Degenerative changes in the nerve cells of the cords of rabbits following somewhat prolonged poisoning by water moccasin venom, are reported by Langmann,[16] and Flexner and Noguchi[17] have demonstrated a true chromatolysis occurring in the isolated cells of several species of *Gastropod,* when treated with rattlesnake or moccasin venom.

SYMPTOMATOLOGY.

The clinical picture seen in actual cases of snake poisoning in man presents such wide variations that its intelligent presentation becomes a matter of some difficulty. The different factors determining the severity of the symptoms naturally have a decided bearing on the mortality and prognosis of the condition and will be given detailed consideration in that connection. The great differences in the toxic properties of the colubrine and viperine venoms are well shown by the characteristic differences in the symptoms of poisoning by the coral snakes and pit vipers, differences sufficiently great to necessitate their separate consideration. The symptoms of crotaline poisoning will be taken up first. It is not to be supposed, however, that all the symptoms enumerated below will occur in every case, for in any particular instance many or nearly all of them may be absent. The attempt has been made to consider all of the important symptoms present in the different cases studied and to indicate, in a general way, the frequency of their occurrence.

The symptoms of snake poisoning are both local and constitutional.

Local symptoms are always present in cases of crotaline poisoning even when evidences of constitutional disturbances are slight or entirely lacking. They are, in addition to the characteristic appearance of the wound, the usual manifestations of a rapidly spreading inflammatory process of severe grade, with markedly hemorrhagic and necrotic tendencies.

The appearance of the wound is, fortunately, almost pathognomonic. Its examination reveals the presence of two, occasionally only one, punctured wounds situated in the center of a rapidly spreading tumefaction. These are the fang punctures, and their size and the distance separating them, serve as a rough indication of the size of the snake causing the injury. The skin around the site of the fang wounds is occasionally found slightly abraded by the fine, retrocurved teeth of both the upper

16. Langmann, G.: Poisonous Snakes and Snake Poisons, Med. Rec., 1900, lviii, 40.

17. Flexner and Noguchi: Jour. Path. and Bacteriol., 1905, x.

and lower jaws. These abrasions are of absolutely no consequence even when made by the teeth of a very large snake. Rarely the fang punctures bleed actively either immediately or at some time after the bite; usually they only exude a bloody serum.

The great severity of the symptoms of the local inflammatory process set up by crotaline venom is characteristic. Pain is usually severe, especially after the swelling becomes extensive and in those cases in which prolonged tight ligation of the bitten part is practiced. The amount of pain caused by the bite itself is variable, probably depending on the size of the fangs and the amount of tearing of the tissues. Swelling is rapid both in its onset and spread, and in cases of any severity, where the lesion is on an extremity, it reaches the trunk within the first twenty-four hours. In some cases the tumefaction is considerable over the lateral half of the body receiving the injection, and in rare instances has been stated to have been general. In cases in which the lesion is on the face or neck the swelling is not only intense, but dangerous *per se*, because of the occurrence of edema of the glottis. This condition was present in a case reported to me by Dr. J. B. Ashford, of Water Valley, Texas. It was relieved by local blood letting, and the patient, an adult male, recovered. Swelling of a degree sufficient to cause spontaneous rupture of the skin is reported in several cases. The skin over the swollen parts is frequently so distended as seriously to endanger its vitality, presenting under these circumstances a peculiar glazed appearance. Discoloration is marked and extensive, spreading, in cases of bites on the extremities, well up on to the trunk. The color is that characteristic of extensive ecchymotic lesions, and may be uniform or patchy in its distribution. In many cases the skin immediately around the bite or over the whole of the bitten limb becomes covered with blebs and bullæ containing a blood-stained serum.

The amount of local necrosis following these extensive changes is variable; some cases escaping it entirely, although a slight superficial slough around the sight of the fang punctures is very common. In other cases, particularly those in which the tissues have had to withstand the devitalizing action of a prolonged ligation in addition to that of the venom, the local sloughing is much more extensive, involving deep as well as superficial tissues, frequently necessitating the loss of fingers or even in rare cases of a whole limb.

The constitutional symptoms present even greater variations in the degree of their severity than do the local manifestations, and every possible gradation is seen between cases resulting fatally in less than an hour and those in which constitutional disturbances is almost entirely

lacking. Usually, however, the prostration is alarming enough. Within a variable period following the bite, usually less than fifteen minutes, during which fright and terror may cause fainting, the patient experiences sensations of vertigo, an inability to use the limbs, and rapidly passes into a state of collapse. The symptoms of this stage differ but little from those of similar conditions due to more ordinary causes. The respiration may be either rapid and shallow, or slow and stertorous. The pulse is rapid, feeble and of very low tension. Blood pressure falls rapidly. The temperature is subnormal, the skin cold and clammy and covered with perspiration. Nausea is usually present and vomiting is a frequent occurrence. Power of voluntary motion is more or less completely absent, and the mind may be more or less clouded. Involuntary evacuations of the rectum and bladder may occur. In cases of ordinary severity, reaction from this primary collapse sets in usually within a few hours and the patient may rapidly pass from a condition exciting the gravest fears to one of comparative safety. This tendency to react promptly and effectively from a prostration of the utmost apparent gravity, irrespective of the line of treatment employed, is quite characteristic, and was first pointed out by Mitchell.[2]

In cases of greater severity progress is neither so rapid nor so favorable. Reaction may fail to occur, the patient sinking rapidly until death ensues.[18] In other cases[19] a tendency toward reaction is manifested by a fuller and less rapid pulse, a clearing of the mind, easier respiration, and a cessation of nausea and vomiting, only to be followed by the occurrence of a secondary collapse which usually proves rapidly fatal. This unfortunate accident has been caused in several cases by too complete and sudden removal of a ligature which was still segregating considerable of the venom from the general circulation. In other instances the cause of the secondary collapse is less obvious, although the result is the same. In the severe cases now under consideration many symptoms are present which are fortunately seen rarely, or only in modified form, in the average run of cases. Among these, the various manifestations of the hemorrhagic tendency induced by the venom are of great interest. In the average case this tendency is shown only by the purpuric discoloration of the skin and subcutaneous tissues of the bitten limb and adjacent portions of the trunk. In other instances the purpuric eruption may be general, and associated with more or less active epistaxis, bleeding from the mouth, hematemesis, hemoptysis, hematuria and hemoglobinuria and bleeding from the rectum, vagina, fang

18. See Cases 3, 4, 8 and 10, Table 2.
19. See Cases 5, 9, 12 and 13, Table 2.

punctures or the wounds made in treatment. A most interesting case, presenting practically all of these symptoms, is reported by Owen.[20] The patient, a young woman, was bitten on the ankle by a snake thought to have been a moccasin. All the hemorrhagic symptoms mentioned above were present except bleeding from the wound. No treatment is mentioned until about twelve hours after the bite, which may account for the severity of the case. The patient recovered in a week. Case 10 in Table 2 also shows conclusively how severe the hemorrhage may be. It is doubtful, however, if these symptoms are dangerous in themselves, and their greatest importance is found in their indicating the increased likelihood of hemorrhagic transudates at vital points. It should be borne in mind that hemorrhages in the heart, pericardium, medulla, brain or other viscera, may be the immediate cause of sudden death, or of various otherwise unaccountable symptoms which may serve to give a most unusual aspect to the clinical picture of a case.

A glance at the constitutional symptoms presented by the fatal cases collected in Table 2 will disclose many interesting manifestations referable to the nervous system. The preservation of a degree of mental clearness quite remarkable when the profound prostration present is taken into consideration, is characteristic in most instances, although in some cases an active delirium is present from the beginning. Delirium, however, is more frequently mentioned as a later symptom and in the great majority of cases is probably an indication of septic infection. Coma seems to be rare except as a terminal event in fatal cases. Great restlessness and jactitation are frequently mentioned; less often a paretic condition of the extremities. General convulsions were noted most often in children, as might be expected, and would seem to be of grave prognostic significance, every case in which they occurred ending fatally. Almost complete cutaneous anesthesia is mentioned in one case, and various paresthesias, such as a sense of constriction in the throat or chest, were noted several times. Symptoms referable to the cranial nerves are seen occasionally. Various disturbances of vision amounting to total blindness, paralysis of the ocular muscles, and ptosis have all been observed. During the stage of primary collapse, the pupil seems to be most frequently dilated, and may fail to react to light. As to whether these and other disturbances of functions are due to a direct action of the venom on the nerve centers involved or to the occurrence of minute central hemorrhages, it is difficult to say. In this connection the case reported by Bailie[21] is worthy of mention. The patient, an

20. Owen, F.: New Orleans Med. and Surg. Jour., 1867, xx, 207.
21. Bailie, A.: Med. Times, London, 1849, xx, 179.

adult male, was bitten on the ankle by a rattlesnake. A tendency toward hemorrhage was shown by the presence of blood in the stools and sputum, and the occurrence of a temporary ptosis, confined to the right side, might well have been caused by a small hemorrhage. A temporary amaurosis was also present in this case. Deafness of brief duration is mentioned in one case.

The findings in regard to temperature, pulse and respiration show little that is typical. When the primary collapse was at all severe the temperature, if mentioned at all, was stated to be subnormal. Fever is noted in a number of cases, but in most instances is undoubtedly septic in character rather than being reactionary, or due to disturbances of the heat regulating center. The pulse is usually stated to have been weak, rapid and lacking in volume, although a slow pulse was present in a few cases. The respirations were most frequently rapid and shallow, in a small number of cases slow and stertorous. The occurrence of hemoptysis has been noted. Pulmonary edema was present in a few cases. It is interesting to note that in Case 10, Table 2, it is definitely stated that the respirations continued after the heart ceased beating, an observation tending to support the statement previously made in regard to the lack of selective action of rattlesnake venom on the respiratory center. On the other hand the experimental findings in regard to the effect of *Ancistrodon* venoms on the respiratory center are strikingly borne out clinically by the case reported by Crum.[22] The patient, a young woman, about 20 years of age, was bitten on the ankle by a copperhead of medium size. Two hours later, the respiration ceased and had to be kept up artificially. This patient finally recovered.

Symptoms from the alimentary and genito-urinary systems are mainly manifestations of the hemorrhagic activity of the venom. Nausea and vomiting are present in almost every case of any severity. The character of the vomitus is rarely mentioned. The presence of blood is noted in some cases, in others it is stated to be bilious. Difficulty in swallowing or a complete inability to swallow was noted occasionally. The violent purging, with blood stained stools or even pure blood,[23] is more likely to be due to the action of the venom than the simple diarrhea occasionally noted, which may well be septic in character. Retention of urine requiring catheterization was present in a few cases. I have been unable to find the report of a single urinalysis in any of the cases

22. Crum, C. W. R.: Treatment of the Bites of Copperhead Snakes by Local Freezing Combined with Frequent Applications of Potassium Permanganate Solution, Jour. Am. Med. Assn., 1906, xlvi, 1433.

23. See Case 10, Table 2.

studied, beyond vague references to the amount passed and the amount of blood present. It is more than likely that investigation along this line would disclose the presence of a nephritis in cases of any severity and duration.

All that has been said above applies to the symptomalogy of crotaline poisoning exclusively. Knowledge covering the symptoms of colubrine poisoning in the United States must be based largely on reasoning from analogy, only seven cases being mentioned in the literature and these with a paucity of detail sufficient to make them practically worthless. It need only be said here, that bites by the coral snakes are followed by a characteristic absence of local symptoms and by a profound prostration, very frequently terminating fatally, probably from a paralysis of the respiratory center in the medulla. The symptoms presented by two fatal cases of coral snake bite will be found under Cases 14 and 15, Table 2, and it will be seen that there is no reason for believing that the action of the venom of these snakes differs essentially from that of other colubrine venoms. While cases of colubrine poisoning will undoubtedly continue to be so rare in this country as to be practically negligible, the following notes on the seven reported cases are appended for the sake of getting them recorded in medical literature. Of the seven cases only two have been previously mentioned in purely medical literature, one by Barringer[24] and one by Yarrow.[25] Stegner[1] collected six cases, including the two mentioned above. These were originally reported by True,[26] Coe[27] and Loennberg.[28] I am indebted to Dr. Menger, of San Antonio, for calling my attention to the case, mentioned by him in a paper read before the Scientific Society of San Antonio.[29] In a personal communication from Dr. C. L. Randall, of Altamonte Springs, Fla., mention is made of one other case, ending fatally.

Table 2 contains a tabular statement of the clinical data available in fifteen fatal cases of snake poisoning, three of which, Cases 1, 2 and 4 have been previously tabulated by Mitchell.[2]

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24. Barringer, P. B.: The Venomous Reptiles of the United States, with the Treatment of Bites Inflicted by Them, Tr. South. Surg. and Gyn. Assn., 1891, Philadelphia, 1892, iv, 283; also Gaillard's Med. Jour., 1892, lv, 7.

25. Yarrow, H. C.: The Recurrence of Symptoms of Poisoning After Snake-bite, Med. News, Philadelphia, 1887, L., 623.

26. True: Am. Naturalist, 1883, xvii, 26.

27. Coe: Scient. Am., 1891, lxiv, 401.

28. Loennberg: Proc. U. S. Nat. Mus., xvii, 334.

29. Menger: Bull. Scient. Soc., San Antonio, 1905, i, 11.

TABLE 2.—CLINICAL DATA IN FIFTEEN FATAL CASES OF SNAKE POISONING.

Reporter.	Patient.	Snake.	Wound.	Duration.	Local Symptoms.	Constitutional Symptoms.
1. Pihorell[13]	Male adult about 50 years.	Captive rattlesnake.	Hand, 2 bites, 3 fang wounds.	Nine hours.	Slight swelling, and discoloration.	Faint[ed] after use of cautery; great prostration following removal of ligature, pulse 50, weak, later rose to 110. Respiration noisy, mind clear, difficult deglutition, pupils contracted, swelling of lips.
2. Horner[14]	Adult male, chronic alcoholic.	Captive rattlesnake.	Elbow	About 18 hours.	Itching followed by pain and swelling.	Bitten in afternoon. Next morning vomiting, involuntary stools of dark bilious color, pulse thready, respiration natural and easy, one general convulsion, great prostration, violent abdominal pains, mind clear until death.
3. Clarke[30]	Adult male about 50 years, had leprosy and elephantiasis.	Captive rattlesnake.	Hand, over fourth and fifth metacarpal bones.	Twenty-four hours.	Pain and coldness in hand first noticed. Rapid swelling and increase of pain which extended to chest. Some discoloration.	In order of occurrence: sensation of fullness in jugulars, numbness over whole body, general tremor, difficulty of speech, sense of constriction in throat, somnolency, chilliness, difficulty of deglutition, loss of use of arm, slight epistaxis, which continued, bleeding from pustule under arm, difficult respiration, salivation, frequent micturition, great anxiety and restlessness, bloody urine, involuntary movements of right thumb and left leg, convulsions, death. Pulse ranged around 100 and was full until near the end.
4. Post[31]	Male about 40 years, a physician.	Captive rattlesnake.	Last phalanx, middle finger.	About 5 hours.	Jet of blood from wound immediately following bite. Rapid swelling and discoloration extending up arm.	Two and a half hours after bite, pulse 80, medium strength and fullness. Third hour, pulse absent at wrist, coma. Fifth hour, death.
5. Alexander[32]	Small child.	Rattlesnake (Crotalus).	Near tendo achilles.	Eighteen hours.		Rapidly fatal collapse following removal of ligature sixteen hours after bite.
6. Kunkler[33]	Boy of 6 years.	Copperhead	Little toe.	Death on fourth day.	Rapid swelling. Second day entire limb swollen, foot a shapeless mass, large vesicles over entire limb, course of lymphatics indicated by red lines: Third day gangrene of entire foot extending rapidly, inflammation, extending over groin and scrotum.	First day: nausea, cold skin, rigors, feeble pulse. Second day: high fever, rigors, constant delirium, tongue dry and red, diarrhea. Third day: condition worse, delirium continued. Fourth day: convulsions and death.
7. Shapleigh[34]	Adult male.	Captive rattlesnake, large southern species.	Single bite on index finger.	Forty minutes.	Quivering of bitten part.	Great excitement, sense of impending death, coma, stertorous breathing.
8. Rivers[35]	Negro boy, 7 years.	Rattlesnake	Probably upper extremity.	Three hours.	?	Vomiting within three minutes. Spasmodic movements of eye muscles, considerable motor excitability, unconsciousness, coma and death.
9. Comfort[36]	Boy 6 years, weighing about fifty pounds.	Rattlesnake, length about 4 feet.	Back of hand, 2 fang punctures.	Seventeen hours.	Four hours after bite area immediately around wound not much swollen but apparently gangrenous. Arm greatly swollen and discolored, fingers semiflexed.	One p. m., four hours after bite: Patient delirious, hearing impaired, blindness, ptosis, paralysis of superior recti muscles, pupils dilated and insensitive to light, little suffering, marked prostration, no pulse at wrist, respiration 30, temperature 96.8. During afternoon: Repeated vomiting, micturition frequent at first, then less often, urine pale, diarrhea, excessive thirst, great restlessness and jactitation, some paresis of both upper and lower extremities. Three p. m.: Some reaction, pulse felt at wrist, mind clear, hearing and sight normal, complained of pains, felt sleepy, temperature 96.5. During night pulse weakened, convulsions, death at 2 a. m.
10. Spalding[15]	Adult male.	Large Crotalus adamanteus, captive.	Hand between first and second metacarpal bones.	Twenty-seven and a half hours.	Rapid swelling, great pain, discoloration reaching chest, enlargement of axillary glands, hand cold, free bleeding from incisions.	Fainting, vomiting within a half hour. Three hours after bite: cold clammy skin, great anxiety, mind clear, pulse rapid, almost imperceptible, respiration hurried and labored, great restlessness, sense of constriction across chest and pain in abdomen. Fourth hour: involuntary evacuations from bowels, finally becoming nothing but pure blood, vomiting of pure blood, pupils dilated and sluggish, voice husky and weak, radical pulse barely perceptible, great thirst, restlessness. Pulse became weaker and weaker, speech difficult, marked prostration and mental depression, death. Heart ceased beating before respirations.
11. Brewer[37]	Boy 7 years.	Rattlesnake	Finger	Death on fifth day.	Enormous swelling and bleb formation up to trunk. Great pain.	First day: breathing difficult, uncertain heart action, patient rational, convulsive movements. Second day: active delirium, trismus, high arterial reaction, fever, great pain. Third day: better, took nourishment, acted rationally at times. Fourth day: fall in temperature, swelling spreading over body, fifth day: death.
12. Crouse[38]	Negro boy, 5 years.	Crotalus adamanteus, 5½ feet long.	Dorsum of hand.	Six and a half hours.		Two and a half hours after bite: great prostration, cold extremities, pulse 56, scarcely perceptible at wrist, respiration shallow, 48 per minute, abundant moist rales in lungs, temp. 97, pupils contracted, conjunctivæ injected, vomiting, general cutaneous anesthesia. Slight reaction followed injection of strychnin. Collapsed after relaxation of ligature, pulse absent at wrist, respiration more rapid, mind clear, retention of urine, death in convulsions.
13. Lewis[39]	Male, 14 years.	Large rattlesnake.	Calf of leg, juncture of upper and middle thirds. Both fangs penetrated full length.	Six hours.	Two hours after bite great swelling of limb, considerable pain, ecchymosis around fang wounds.	Two hours after bite: pulse 140 and weak, cold extremities, considerable nausea and vomiting. Reaction followed treatment, pulse slower and better volume, extremities warm, mind clear, no pain. After about two hours became more rapidly, pulse weak, about 150, respiration rapidly reached 65. Bowels moved repeatedly, restless, mind clear, death.
14. True[28]	Adult male.	Coralsnake	Finger	Twenty-four hours.	None present.	Sense of glowing heat over whole body, great prostration, slow, feeble pulse, total suppression of urine, no unconsciousness.
15. Coe[27]	Adult male.	Coralsnake. E. fulvius.	Hand	Eighteen hours.	Pain in hand and arm half hour after bite.	Drowsiness, dull pain in head, sense of fullness in eyelids, ptosis.

30. Clarke: Lancet, 1838-39, i, 443.
31. Post: Buffalo Med. Jour. and Month. Rev., 1848, iv, 115.
32. Alexander: St. Louis Med. and Surg. Jour., 1855, xiii, 116.
33. Kunkler: Cincinnati Lancet and Observer, 1859, new series ii, 662.
34. Shapleigh: Am. Jour. Med. Sc., 1869, lvii, 392.
35. Rivers: South. Med. Record, 1874, iv, 505.
36. Comfort: Philadelphia Med. Times, 1878, ix, 77.
37. Brewer: Kansas Med. Jour., 1897, ix, 57.
38. Crouse: The Virginia [illegible] 1901-02, xi, 413.
39. Lewis: Jour. Am. [illegible]

TABLE 2.—CLINICAL DATA IN FIFTEEN FATAL CA

	Duration.	Local Symptoms.	
es, 3 s.	Nine hours.....	Slight swelling, and discoloration.	Fainted after use of ca pulse 50, weak, later deg atition, pupils co
.....	About 18 hours.....	Itching followed by pain and swelling.	Bitter in afternoon. No color, pulse thready, great prostration, viol
fourth etacar-	Twenty-four hours.	Pain and coldness in hand first noticed. Rapid swelling and increase of pain which extended to chest. Some discoloration.	In order of occurrence: body, general tremor somnolency, chilliness epistaxis, which con respiration, salivation bloody urine, involunt death. Pulse ranged
, mid-	About 5 hours.....	Jet of blood from wound immediately following bite. Rapid swelling and discoloration extending up arm.	Two and a half hours af hour, pulse absent at
hilles.	Eighteen hours.....	.....	Rapidly fatal collapse f
.....	Death on fourth day.	Rapid swelling. Second day entire limb swollen, foot a shapeless mass, large vesicles over entire limb, course of lymphatics indicated by red lines: Third day gangrene of entire foot extending rapidly, inflammation, extending over groin and scrotum.	First day: nausea, col rigors, constant deliri tion worse, delirium
index	Forty minutes.....	Quivering of bitten part.	Great excitement, sens
per ex-	Three hours.....	.....	Vomiting within three erable motor excitabili
nd, 2 ures.	Seventeen hours....	Four hours after bite area immediately around wound not much swollen but apparently gangrenous. Arm greatly swollen and discolored, fingers semiflexed.	One p. m., four hours af ptosis, paralysis of su light, little suffering, temperature 96.8. Dur at first, then less ofte ness and jactitation, Three p. m.: Some rea normal, complained of weakened, convulsions
en first d meta- es.	Twenty-seven and a half hours.	Rapid swelling, great pain, discoloration reaching chest, enlargement of axillary glands, hand cold, free bleeding from incisions.	Fainting, vomiting withi great anxiety, mind hurried and labored, g pain in abdomen. Fou becoming nothing but sluggish, voice husky restlessness. Pulse be tration and mental de tions.
.....	Death on fifth day.	Enormous swelling and bleb formation up to trunk. Great pain.	First day: breathing dif sive movements. Secon fever, great pain. Thi times. Fourth day: fa day: death.
and....	Six and a half hours.	.....	Two and a half hours af scarcely perceptible at moist rales in lungs, t iting, general cutaneo strychnin. Collapsed respiration more rapid,
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.....	Twenty-four hours.	None present.....	Sense of glowing heat o total suppression of u
.....	Eighteen hours.....	Pain in hand and arm half hour after bite.	Drowsiness, dull pain in

34. Shapleigh: Am. Jour. Med. Sc., 1869, lvii, 392.
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36. Comfort: Philadelphia Med. Times, 1878, ix, 77.
37. Brewer: Kansas Med. Jour., 1897, ix, 57.

Constitutional Symptoms.	Treatment.	Remarks.
of cautery; great prostration following removal of ligature, later rose to 110. Respiration noisy, mind clear, difficult ls contracted, swelling of lips.	Temporary ligation done immediately. Actual cautery in 18 minutes. Olive oil, leeches to throat.	For autopsy see Case 2, Table 1.
a. Next morning vomiting, involuntary stools of dark bilious eady, respiration natural and easy, one general convulsion, violent abdominal pains, mind clear until death.	Local blood letting, ammonia and olive oil internally.	Patient intoxicated when bitten. For autopsy see Case, 3, Table 1.
ence: sensation of fullness in jugulars, numbness over whole emor, difficulty of speech, sense of constriction in throat, liness, difficulty of deglutition, loss of use of arm, slight continued, bleeding from pustule under arm, difficult ration, frequent micturition, great anxiety and restlessness, oluntary movements of right thumb and left leg, convulsions, ged around 100 and was full until near the end.	Practically none.....	Patient allowed himself to be bitten in hope of curing leprosy. Decomposition very rapid.
urs after bite, pulse 80, medium strength and fullness. Third nt at wrist, coma. Fifth hour, death.	Immediate suction, excision of bite in less than half an hour; cautery and ligation. Brandy and ammonia carbonate by mouth and rectum.	Spurt of blood may have indicated intravenous injection of a part of the venom.
apse following removal of ligature sixteen hours after bite.	Ligature, no incisions. Intoxication with whiskey.	Death was attributed to too sudden removal of ligature.
, cold skin, rigors, feeble pulse. Second day: high fever, delirium, tongue dry and red, diarrhea. Third day: condiium continued. Fourth day; convulsions and death.	Free incision, labial suction, solution of iodin and potassium iodid injected locally, opium and ammonia.	Death undoubtedly due to sepsis.
sense of impending death, coma, stertorous breathing.	Cauterized with pure nitric acid within two minutes. Free incision and ligation within twenty minutes. Alcohol internally.	Death may have been due to cerebral hemorrhage.
ree minutes. Spasmodic movements of eye muscles, considtability, unconsciousness, coma and death.	.....	.....
urs after bite: Patient delirious, hearing impaired, blindness, of superior recti muscles, pupils dilated and insensitive to ring, marked prostration, no pulse at wrist, respiration 30. During afternoon: Repeated vomiting, micturition frequent often, urine pale, diarrhea, excessive thirst, great restlesstion, some paresis of both upper and lower extremities. e reaction, pulse felt at wrist, mind clear, hearing and sight ed of pains, felt sleepy, temperature 97.5. During night pulse isions, death at 2 a. m.	Immediate incomplete ligation and whiskey internally. Four hours after bite, tight ligation, ammonia hypodermically and by mouth, whiskey every hour. Ligature loosened seven hours after bite.	Death attributed to premature loosening of ligature by child's mother.
within a half hour. Three hours after bite: cold clammy skin, ind clear, pulse rapid, almost imperceptible, respiration ed, great restlessness, sense of constriction across chest and . Fourth hour: involuntary evacuations from bowels, finally but pure blood, vomiting of pure blood, pupils dilated and sky and weak, radical pulse barely perceptible, great thirst, se became weaker and weaker, speech difficult, marked prosal depression, death. Heart ceased beating before respira-	Wound incised three times. Enormous doses of whiskey. Whiskey and ammonia hypodermically.	For autopsy see Case 4, Table 1.
ng difficult, uncertain heart action, patient rational, convul- Second day: active delirium, trismus, high arterial tension, . Third day: better, took nourishment, acted rationally at ay: fall in temperature, swelling spreading over body. Fifth	Prompt ligation, excision of bite, labial suction. General stimulation with whiskey, and strychnin hypodermically.	Death evidently due to sepsis.
urs after bite: great prostration, cold extremities, pulse 162, ble at wrist, respiration shallow, 48 per minute, abundant gs, temp. 97, pupils contracted, conjunctivae injected, vomtaneous anesthesia. Slight reaction followed injection of psed after relaxation of ligature, pulse absent at wrist, rapid, mind clear, retention of urine, death in convulsions.	Ligature within twenty minutes. Potassium permanganate in the wound. Strychnin hypodermically.	Death probably due to too sudden relaxation of ligature.
te: pulse 140 and weak, cold extremities, considerable nausea eaction followed treatment, pulse slower and better volume, , mind clear, no pain. After about two hours became worse eak, about 150, respiration rapidly reached 65. Bowels moved ss, mind clear, death.	Immediate ligation. Two hours after bite: crucial incision of wound, labial suction, moist carbolic dressing, second ligature relaxed intermittently, artificial heat, strychnin and adrenalin, 1 to 1000, hypodermically, aromatic spirits of ammonia by mouth.	Death in spite of skilled treatment.
eat over whole body, great prostration, slow, feeble pulse, of urine, no unconsciousness.	.....	.....
ain in head, sense of fullness in eyelids, ptosis.....	.....	.....

92.

77.

38. Crouse: The Venomous Snakes and Spiders of Texas, Texas Med. News, 1901-02, xi, 413.

39. Lewis: Jour. Am. Med. Assn., 1906, xlvii, 2012.

COMPLICATIONS AND SEQUELÆ.

The frequency with which crotaline poisoning is complicated by local or general septic infection, and the severity of these conditions when present, have received but scant attention in the literature. It is obvious that a marked predisposition to infection must be present. Locally, we are dealing with a greater or less amount of necrotic tissue, being gradually separated from the body by the usual process of sloughing. Those tissues in the neighborhood of the wound which have escaped death must of necessity be devitalized from the powerful and concentrated action of the venom, and in a large number of cases, from the effects of a prolonged ischemia induced by too light ligation. Great softening, edema, and infiltration with extravasated blood are also present. In addition to the general systemic depression which must follow such a severe intoxication, the positive reduction or total destruction of antibactericidal properties of the blood must be taken into consideration. It is little wonder, then, that septicemic and pyemic processes are so frequently observed clinically, but it is difficult to understand the scant consideration which has been accorded this phase of the subject in the literature. While the symptoms, course and treatment of these infections present nothing unusual, it must be pointed out that chills, high fever, full bounding pulse, and active delirium, stated to be present in so many cases, mean infection and not the venom intoxication to which they are, in the majority of instances, attributed. The frequency of this complication, and the necessity for guarding against it can not, in my opinion, be too strongly emphasized.

In addition to the infections beginning in the tissues around the wound and becoming localized there, or involving the body generally, there are undoubtedly various other infective processes, terminal or otherwise, which have escaped notice clinically. McFarland[40] observed a fatal pneumonia in one of the horses used in his attempt to prepare an effective anticrotaline serum, and pneumonia and other infectious diseases may reasonably be supposed to occur in man.

For the following report of a most interesting case, tetanus complicating snake bite, which so far as my reading goes is unique in medical literature, I am indebted to Dr. W. E. Hawkins, of Bayou Chicot, La. The patient, an adult male, was bitten on the thumb by a large rattlesnake. He received no medical attention, but did very well for about a week, when he first came under observation with well-developed symptoms of tetanus from which he died in two days. The fact that this

40. McFarland, H. J.: Some Investigations on Antivenene, Jour. Am. Med. Assn., 1901, xxxvii, 1597.

patient received no medical attention immediately after the bite renders it likely that the organism was introduced on the fangs of the snake rather than during the local treatment of the wound.

Deformity following snake bite is seen with considerable frequency in the form of fibrous ankylosis of the interphalangeal joints in cases in which the lesion is on a finger. Many such cases are reported. It would seem that extensive deformity might be reasonably expected to follow the cicatrization of the areas of extensive sloughing of superficial tissues and even of muscles, noted occasionally, but no such cases are reported. The extent and seriousness of this sloughing in some instances is well known in the case reported by Walker.[41] A man 35 years of age was bitten by a water moccasin on the dorsum of the hand over the third and fourth metacarpal bones. The accident happened on Sunday morning, the patient drank some whisky and tried to reach the house of a neighbor but fell, and lay all day in the sun, not being found until night. He was first seen by a physician on Wednesday, when the tissues around the bite were in a gangrenous condition. The sloughing became so extensive that the forearm was amputated, the patient making a good recovery. Permanent enlargement of the bitten limb is reported by Jones[42] in the case of an adult male negro bitten on the leg by a water moccasin. Mr. Wood of the Smithsonian Institution has reported to me a case of permanent hypertrophy of the thumb in a boy of twelve, bitten on this member by a small ground rattler, *S. miliarius*. Dr. C. W. Lindner, of Anthony, Fla., reports to me the following interesting and unusual case of deformity following the bite of a rattlesnake. The patient, a boy of ten or twelve, was bitten on the forearm a few inches above the wrist. When recovery was assured the arm was placed in splints and put up in a sling. The child's parents removed the splints, however, and a bow-shaped curvature of both bones resulted. This may have been a case of spontaneous fracture.

Anemia of considerable severity and duration has been noted as a sequel in a few cases. Crum[22] reports such a case following the bite of a copperhead. The patient, an adult female, had previously been in good health and ultimately made a good recovery.

A case of permanent although partial amaurosis is reported by Boseman.[43] The patient was a boy nine years of age bitten on the ankle by a ground rattler. There was considerable suppuration and sloughing

41. Walker, E. M.: Am. Jour. Med. Sc., 1858, xxxvi, 568.

42. Jones: Med. Rec., 1868-69, iii, 289.

43. Bozeman, N.: A Case of Amaurosis from Snake-bite, New Orleans Med. and Surg. Jour., 1849-50, vi, 739.

in this case and as the blindness did not develop until five or six weeks after the injury there is naturally a question as to whether it should be attributed to the direct action of the venom or to the resulting infection.

A belief in the possibility of a periodical recurrence of some of the symptoms of snake poisoning at varying intervals after the original injury, is firmly fixed in the popular mind. *A priori* reasoning would certainly seem to justify the categorical denial of such a possibility. Venom is an albuminous fluid, which from the very nature of things must, after its injection into the living body, either bring about the death of the organism or be itself speedily destroyed. It is therefore impossible to conceive of its remaining latent in the body to be the cause of future local or systemic disturbances. If, then, such occurrences have really been observed they must be accounted for on some grounds other than a latent action of the venom originally injected. Cases reported as recurrences in which the symptoms consist only of vague pains felt in the neighborhood of the wound at irregular intervals, may readily be due to any of the well known factors causing painful cicatrices. In these cases, however, the element of periodicity is lacking. I am perfectly willing to submit the evidence in the case and let the reader draw his own conclusions.

Yarrow[25] in 1887 collected all the alleged cases of recurrence up to that date and added two cases which had come under his own observation. I have found no additional cases worthy of mention reported since the time of Yarrow's article. Of the cases collected in this paper, those of Sweeney,[44] Stockbridge[45] and Coleman[46] have little to recommend them for consideration. Sweeney, for instance, reports a case, in which a condition suspiciously like an ordinary bone felon is attributed to the bite of a copperhead on the same finger thirty years perviously. Both of the cases which came under Yarrow's own observation are of considerable interest. From the original report[47] of the first there can be no doubt that there was considerable infection present. Of the subsequent history of this case Yarrow says: "The case of a photographer, bitten by a copperhead, . . . I have watched carefully from 1883 to 1886, the last attack commencing on May 30, the anniversary of his injury, and lasting over a week. His condition about the acme of the attack was as follows: Pulse quick; complains of general malaise; pain and stiffening in the bitten finger, which extends up the arm; surface

44. Sweeny: Cincinnati Lancet and Observer, 1860, new series, iii, 318.
45. Stockbridge: Boston Med. and Surg. Jour., 1843, xxix, 40.
46. Coleman: Virginia Clin. Rec., 1872-73, ii, 137.
47. Yarrow: Am. Jour. Med. Sc., 1884, new series, lxxxvii, 422.

of hand shows bluish mottling, with lines of redness extending as far as the shoulders along the lines of the lymphatics. He had slight chilly sensations, and some fever. Obliged to quit work, as he could not concentrate his attention to it. Has taken nothing but whisky and quinin. These notes were read to him, and he stated that they represent fairly his condition at each recurring period since the bite." The second case was that of an adult male bitten on the finger by a coral snake *(Elaps fulvius)* in 1882. Each subsequent year at approximately the anniversary of the bite a small abscess formed in the bitten finger, from which the nail would be lost.

The case of Piffard[48] is undoubtedly the most interesting in the literature. It is reported in great detail. At the first examination of the patient there was noted a tendency toward contraction of the flexor tendons of the right forearm and the presence of a vesicular eruption on the skin between the thumb and index finger of the right hand. Inquiry elicited the information that the patient, a young woman of nineteen, had been bitten on the thumb by a rattlesnake several years previously. At the time, in addition to the usual symptoms there had been a contraction of some of the flexor tendons and an inability to extend the hand. At regular periods of three months the patient had noticed the appearance of a vesicular eruption over the metacarpal bone of the thumb, associated with a "beating" pain and contractures of the flexor tendons. The woman's husband confirmed her statement and Piffard himself observed attacks occurring consecutively in March, June and September and on several subsequent occasions. The interval between attacks gradually became longer, and when last seen the patient had had no attacks during a period of seven or eight months. The total duration of these strange phenomena was over ten years.

In this connection, it may not be amiss to transgress the limitations of the subject to American serpents, in order to mention the very interesting case of Demeurat.[49] His patient was a young woman 26 years of age, who was bitten in May, 1824, by the common European viper, *Vipera berus*. In addition to the more usual symptoms a bullous eruption made its appearance on the skin of the bitten part and did not entirely disappear until November of the following year. In the last part of May, 1826, and at about the same time for 39 consecutive years,

48. Piffard, H. G.: Periodical Vesicular Eruption Following the Bite of a Rattlesnake, Med. Rec., N. Y., 1875, x, 62.

49. Demeurat: Observations d'accidents developpés à la suite d'une morsure de vipère, Gaz. hebdom. de méd., 1863, x, 736.

a similar eruption made its appearance, lasting about six weeks, and preceded by lassitude, anxiety, nausea, headache, and other evidences of constitutional disturbance.

DURATION.

Like everything else connected with the subject, the duration of the illness following snake bite is subject to the widest variations. In the great majority of cases recovery from the constitutional disturbance is complete in two or three days and many times in a few hours. The entire restoration of the tissues around the bite to a normal condition usually takes longer, the exact time taken depending mainly on the amount of necrosis and sloughing and whether or not infection occurs. Tuten[50] reports a case following the bite of a rattlesnake, in which the ulcerated surface left after the separation of the sloughs was over a year in healing. There can be no doubt that the cases of prolonged illness so frequently reported are septic in character, and rarely if ever due to the primary action of the venom. The duration of the fatal cases shows much less variation, although largely influenced by the same factors. Of the seventy-eight fatal cases in the series the time of death was noted with considerable accuracy in fifty cases. An analysis of these cases is presented in Table 3, and for comparison the findings given by Fayer[51] in a similar analysis of sixty-five cases of cobra poisoning. The rather striking similarity is of considerable interest.

TABLE 3.—DURATION OF FIFTY FATAL CASES OF POISONING BY AMERICAN SNAKES COMPARED WITH THAT OF SIXTY-FIVE CASES OF COBRA POISONING.

Duration.	Series of 50 American cases.		Series of 65 cobra cases.
	No. of cases.	Per cent.	Per cent.
Less than one hour	8	16	..
One to six hours	13	26	..
Less than six hours	21	42	46.4
Six to twenty-four hours	18	36	32.5
Less than twenty-four hours	39	78	78.9
Second day	4	8	..
Third to seventh days	4	8	..
Nine days	1	..	..
Seventeen days	1	..	..
Over one month	1	..	..
Longer than twenty-four hours	11	22	21.1

CAUSE OF DEATH.

The action of coral snake venom, as shown in the few recorded cases of bites by these snakes, is sufficiently like that of other colubrine

50. Tuten, J. G.: Jour. Am. Med. Assn., 1897, xxix, 896.

51. Fayer, quoted by Noguchi (8).

venoms, which have been most carefully studied, to render reasonable the belief that death in these cases is usually due to paralysis of respiration.

In crotaline poisoning, however, the cause of death can not be stated with such certainty, and it evidently varies with the time elapsing before its occurence. Cases terminating fatally within a few minutes of the injection of venom are fortunately very rare, but do undoubtedly occur. Roberts[52] reports the case of a boy seven years of age bitten twice by a rattlesnake, once on the hand and once on the cheek, below the eye. The child screamed and pitched forward and was dead before an eye witness of the affair could reach him. Blackwood[53] reports a death occurring within ten minutes in the case of a girl three years of age, bitten on the eyebrow by a large rattlesnake. Unfortunately the reports of these cases are so extremely meager as to preclude the possibility of making deductions concerning the cause of death, from an analysis of the symptoms presented. The possibility of death from shock must be considered, particularly in such a case as that of Roberts. Immediate intravascular thrombosis or the occurrence of hemorrhages in the heart or central nervous system would, of course, afford a satisfactory explanation. In Blackwood's case, however, the blood was found after death to be perfectly incoagulable. As I have stated, I am very skeptical in regard to the possibility of crotaline venom causing immediate intravascular thrombosis in man, with the possible exception of cases similar to the two under discussion, in which, it will be observed, both patients were small children, and the location of the bite was extremely vascular.

Death, in the great majority of cases, occurs in the first twenty-four hours, usually during the primary collapse, in a few cases in a state of secondary collapse to which reference has been made. In these cases sudden death may be due to hemorrhage at vital points and the possibility of fatal termination from suffocation, in cases in which the bite is on the face or neck, should be borne in mind. In most instances, however, both experimental and clinical findings point to a combination of general nervous depression and circulatory failure, due to lowered blood pressure, and resulting in secondary respiratory failure, as being responsible for the fatalities. The greater prominence of primary respiratory failure in cases of *Ancistrodon* poisoning has been pointed out.

In those cases in which death occurs days, weeks or even months after the bite, there can be no doubt that sepsis or some of its complications is responsible. It is interesting to note that of the seventy-eight

52. Roberts, J. C.: South. Pract., 1888, x, 374.
53. Blackwood, W. R. D.: Med. Reg., Philadelphia, 1888, iii, 272.

fatalities in the series, eight may be definitely stated to have been due to sepsis. This would indicate that infective processes are responsible for 10.2 per cent. of the fatal cases, probably an underestimate when we take into consideration the lack, in such a large number of cases, of clinical details sufficient to positively exclude sepsis. Rarely, possibly, death in these cases may be due to the necrotic lesions in the various viscera, particularly the liver and kidneys.

DIAGNOSIS.

The question of diagnosis rarely comes up for solution, the history of the case being usually complete. The venomous or innocuous character of the snake causing the injury will require decision in some cases. If the reptile has been killed its identification may be readily made by looking for the characteristic points considered fully in Part I. If the reptile can not be examined dependence must be placed on the appearance of the wound, which also has been previously considered under symptomatology. Only in exceptional cases will the question as to whether the lesion is due to snake bite or some other form of injury, need solution. The wound, in these cases, may be inflicted in the dark, or persons may be bitten when entirely alone, and found only after death, or unconsciousness has supervened. Here, again, the pathognomonic appearance of the wound, together with the presence of ecchymosis and swelling locally, the profound general collapse, and the subnormal temperature will aid in making a correct diagnosis. A case in which the diagnosis lay between erysipelas and snake bite is reported by Thomas.[54] The patient, a boy of four or five years received an injury on his foot while walking through a stubble field known to have been infested with rattlesnakes. The wound consisted of two scratches. Death occurred on the third day, following enormous swelling of the limb, nausea, vomiting, collapse, and subnormal temperature. The case was diagnosed, correctly in my opinion, as one of snake bite.

MORTALITY.

The mortality from the bites of American serpents has never been satisfactorily determined. Mitchell,[2] in 1860 stated that in 57 cases of rattlesnake bite mentioned in the literature, five patients died. This would represent a mortality of 8.7 per cent. Elzey,[55] whose opinion is often quoted, merely estimated that in 15 per cent. of cases of rattlesnake bite in adults, the patients would die, if left untreated. Barringer[24] stated

54. Thomas, J. T.: Med. Rec., New York, 1890, xxxvii, 123.

55. Ellzey, M. G.: The Venomous Snakes of the United States and the Treatment of Their Bites, Virginia Med. Month., 1884-85, ii, 249.

his belief that the mortality from rattlesnake bite would not exceed 10 per cent. and from copperhead bite 1 per cent. The mortality from water moccasin bite, he thought, would fall below even this last figure. There were 78 fatal cases in the total of 740 which I have collected, a mortality of 10.5 per cent. This figure represents the mortality of all species combined, and in my opinion may be accepted as representing with considerable accuracy the actual mortality attending snake bite in the United States, the number of cases on which it is based being considerable, and having been collected from sufficiently varied sources. As tending to prove the accuracy of this rate, it may be stated that the mortality rates for cases collected from the literature and from various private sources were, respectively, 10.2 per cent. and 10.7 per cent., a variation of only 0.5 per cent. The mortality rate for the different species will be given later in considering the effect of species on the prognosis.

PROGNOSIS.

That an extreme degree of variation in the severity of the symptoms of snake poisoning as seen clinically, is one of the most characteristic features of the condition, has been frequently mentioned previously. It is obvious then, that intelligent prognosis in these cases must be based on a knowledge of the factors determining this variation. These may be stated as follows:

1. The amount and toxic quality of the venom injected.
2. The location and character of the injection.
3. The age, sex and resisting powers of the patient.

It will be readily appreciated that these factors influence the outcome of a case mainly because on them depends the rapidity and amount of venom absorption by the system, in proportion to the weight of the patient.

The amount of venom injected in actual cases of snake bite will depend largely on the size of the snake, the length of time during which its supply of venom has been accumulating, and the perfection with which all the muscular acts concerned in the bite are carried out.

The size of the snake naturally determines the size and capacity of the poison glands and their ducts. This is well shown by the figures given by Mitchell,[2] who compared the length and weight of three rattlesnakes with "the amount in water drops which a single gland in each snake was capable of containing." The findings were as follows:

No. 1—Length, 18 inches; weight, 9½ ounces; capacity of gland, 11 drops.
No. 2—Length, 25 inches; weight, 18 ounces; capacity of gland, 19 drops.
No. 3—Length, 49½ inches; weight, 3 pounds 2 ounces; capacity of gland 29 drops.

In the introduction to their later publication Mitchell and Reichert[55] mention a specimen of *C. adamanteus*, eight and one-half feet in length, which at one bite ejected about one and one-half drams of venom, which of course represented the contents of both glands. These brief statements show conclusively that the chances of a large dose of venom having been injected increase proportionately with the size of the snake causing the injury.

On the other hand, the amount of venom in the glands of a snake of only average size may be greater than the amount in the glands of an unusually large reptile which has recently made use of its fangs. The exact rate at which the poison is elaborated is not known, but it is undoubtedly a comparatively slow process not at all comparable to the secretion of saliva. Mitchell[2] mentions a rattlesnake fifty-three inches in length which ejected about fifteen drops of venom from each fang on one day and only one or two drops on the day following. The great difference in the danger attending a bite by this particular reptile, on the two different days, is obvious.

Certain factors in connection with the perfection of the bite are of the greatest importance. In an absolutely perfect bite, the snake succeeds in injecting the full contents of both glands to the depth of the full length of the fangs. In many actual cases this degree of perfection is not attained. No venom at all may be injected; because of the absence of both active fangs, and the immature condition of the first reserve fangs, or because of an insufficient erection of the fangs, causing their convexities rather than their points to strike the bitten surface, thus bending them back into the animal's own mouth into which the venom harmlessly escapes. When the bite is located on a small member like a finger the fangs may straddle the bitten part, or may completely perforate it, in either of which events, of course, little or no venom would enter the tissues. Any of these conditions may affect only one fang, causing the dose of venom to be decreased by one-half. There can be no doubt that in many actual cases, the bite is inflicted with only one fang. Thus in seven bites inflicted on dogs Mitchell[56] found that the wound had been made by two fangs in four cases and by only one in three cases. Numerous cases are reported in which the wound showed the mark of only one fang. Hopkins[57] reports the case of a child bitten three times on the calf, by a copperhead; of the three wounds two were caused by one fang only. It is possible, also, that in some cases there

56. Mitchell, S. W.: On the Treatment of Rattlesnake Bites, with Experimental Criticisms of the Various Remedies Now in Use, N. Am. Med.-chir. Rev., 1861, v, 269.

57. Hopkins: Med. Rec., 1889, xxxvi, 431.

may be an escape of venom around the fang instead of through the poison canal, because of some inaccuracy in the approximation of the duct from the gland and the upper orifice of the poison canal of the fang, in which case, of course, the amount of venom would be correspondingly decreased.

It will be readily seen that all the factors which have been given consideration above affect the prognosis because they have a most direct bearing on the dose of poison administered, and therefore, are of the greatest importance. Unfortunately the most important point, the probable amount of venom in the glands, will be known only in very exceptional cases, as when the snake has been for some time in captivity and the time elapsing since a previous bite is known. An examination of the wound, however, will frequently give a clue as to the perfection of the bite and, therefore, some idea as to whether or not the full contents of both glands could have been injected. In addition, if the marks of both fangs are present, the distance separating them gives a rough idea of the size of the snake. In cases in which this is known more accurately it becomes a most important factor in the prognosis.

The toxic qualities of the venom injected are, of course, of very considerable importance in determining the outcome of a case. These vary as has been pointed out, with the species of the snake, but it is doubtful if the season of the year determines any increase or decrease in the toxicity of the venom, as is frequently seen stated. It must be borne in mind, however, that the species not only affects the toxic properties of the venom, but to a large measure the size of the snake, and therefore the amount of venom injected. For this reason the mortality following the bites of the pit vipers does not vary with the species as might be expected from the relative toxicity of the venom as shown for guinea-pigs. In Table 4 are given the findings in 624 cases of snake bite in which the species was known more or less definitely.

TABLE 4.—EFFECT OF THE SPECIES OF THE SNAKE MORTALITY IN 624 CASES.

Genus or species.	Number cases.	Number fatal cases.	Percentage mortality.
Rattlesnakes, genus *Crotalus*	38	6	15.7
Rattlesnakes, genus *Sistrurus*	20	0	0
Rattlesnakes, genus not given	350	42	12
All rattlesnakes	408	48	11.7
Copperheads	97	5	5.1
Water moccasin	53	9	16.9
Crotaline snakes, species not given	58	1	..
All species	616	63	10.2
Coral snakes	8	6	75.0
All crotaline snakes	624	69	11.0

A more detailed study of these figures is necessary and interesting.

It is unfortunate that the exact species of rattlesnakes is not more frequently mentioned in reporting cases, for practically nothing is known concerning the relative toxicity of the venoms of different species and some light might be thrown on the subject from practical sources if the number of cases were large enough. The small size of the ground rattlers as compared with that of the larger species of *Crotalus*—and it is the larger species which are responsible for most of the bites—readily accounts, however, for the different mortality rates shown in Table 4. There can be little doubt that bites by the ground rattlers, particularly *S. miliarius*, are practically never fatal to adult man except, possibly, through septic complications, and the species of this genus are our least dangerous poisonous snakes. The mortality rate given for all rattlesnake cases, 11.7 per cent. is, in my opinion, based on a sufficiently large series of cases to be accepted as approximately correct.

There were five fatalities in the 97 cases of copperhead bite in the series, representing a mortality rate of 5.1 per cent. Of the 5 fatal cases, 2 were in children, both being reported by Kunkler. The first case,[58] occurring in a boy of nine years, received no treatment. The fatal termination in the second case, a boy of six years, was undoubtedly due to sepsis.[59] The remaining three cases were reported to me, two by Dr. C. W. R. Crum, of Brunswick, Md., the other by Dr. C. B. Turner, of Bluemont, Va. All the patients were adult males and in every case the amount of bad whiskey taken by the patient was considered by the reporter to have been a decided factor in the fatal outcome. These facts make it clear that the prognosis in copperhead bite is very good, even in children, and it is very doubtful if the bite of this specie is ever fatal to adults in uncomplicated cases. Such a finding is of interest when the greater toxicity of this venom, as compared with that of the rattlesnake, is considered, and it is to be explained on the ground of the much smaller average size of this species. There seems to be some reason for believing that the fangs in the copperhead are both absolutely and relatively smaller than in the other pit vipers and this fact would, of course, assist in explaining the comparatively slight danger of its bite, the injection of the venom being more superficial.

The mortality of 16.9 per cent. in the 53 cases of water moccasin bite in the series points at once to the dangerous character of this snake, and bears out in a suggestive way the experimental findings in regard to the toxicity of its venom. That the mortality is not greater is again due, in a large measure, to the question of size. The water moccasin, while

58. Kunkler, G. A.: Med. Counselor, Columbus, 1855, i, 481.
59. See Case 6, Table 2.

averaging much larger than the copperhead, certainly never attains the large size of some of the larger species of Crotalus. Ellzey[55] considers this reptile our most dangerous snake, an unenviable distinction which must, in my opinion, be accorded to *C. adamanteus*. In a large series of cases, however, the mortality following moccasin bite would certainly exceed that of all rattlesnake bites taken collectively. It is fortunate that the habits and somewhat limited distribution of this species make its bite an infrequent occurrence.

The frightful mortality following the bites of the coral snakes, 75 per cent., is based on a number of cases entirely too small to be of great accuracy, and is undoubtedly excessive, since it exceeds that given for cobra bite, 25 to 45 per cent. (Calmette). It serves, however, to emphasize the dangerous character of this snake which was long considered to be almost harmless to man, and the necessity for its correct differentiation from the non-venomous species which simulate its general appearance. Being small snakes the dangerous nature of coral snake venom, a characteristic colubrine feature, is made evident.

All those factors in the prognosis which have been considered have had to do with the amount and toxic quality of the venom injected. The factors contributed by the location and nature of the injection, and the resisting powers of the patient now claim attention.

TABLE 5.—EFFECT OF LOCATION OF THE BITE ON MORTALITY IN 347 CASES.

Location of bite.	Number cases.	Number fatal cases.	Percentage mortality.
Finger	61	6	9.8
Hand and wrist	67	13	19.0
Arm	11	2	18.1
Upper extremity, exact location not given	9	4	....
Upper extremity, total cases	148	25	16.8
Foot and ankle	123	7	5.6
Leg	55	8	14.5
Lower extremity, exact location not given	5	1	....
Lower extremity,	183	16	8.7
Extremity, exact location not given	4	..	....
Both extremities, total cases	335	41	12.2
Throat	1	0	....
Tongue	1	1	....
Scalp	2	0	....
Cheek	3	3	....
Eyebrows	1	1	....
Lip	2	1	....
Vulva	1	1	....
Penis	1	0	....
Head and trunk, total cases	12	7	58.3
All locations, total cases	347	48	13.8

A study of the varying mortality rates for bites on different portions of the body, shown in the analysis of 347 cases presented in Table 5,

discloses many points of considerable interest. It has long been known that bites on the trunk and head are more dangerous than those on the extremities, and this is confirmed by the mortality rates given in Table 5, which are, respectively 58.3 per cent. and 12.2 per cent. The number of cases of bites on the head and trunk is so small, that the rate given, may well be inaccurate and is probably somewhat excessive. The great danger of bites here as compared with those elsewhere is clearly demonstrated, however. The reasons for such a difference are to be looked for in the greater vascularity of the head and neck, which determines a more rapid absorption and an increased danger of the venom being injected directly into a blood vessel, and the difficulty of taking effective measures by means of ligatures to localize the venom at the seat of injection. It is fortunate that the bite is located on the head or body in such a small number of cases, 3.4 per cent. in the 347 cases in the series.

The striking difference in the mortality of bites on the upper and lower extremities is, so far as my knowledge goes, here pointed out for the first time. It will be seen that the rate for the upper extremities, 16.8 per cent., is practically double that for the lower, 8.7 per cent. The difference in the rates for the hand and wrist, and foot and ankle, 19.0 per cent. and 5.6 per cent. respectively, is even more striking. Therapeutic measures intended to limit the amount of venom absorption may be applied with equal effectiveness to either extremity and the reasons for the greatly decreased danger attending bites on the foot and leg must be accounted for on other grounds. There can be no doubt that the more active circulation of the upper extremity, the greater number and prominence of the superficial veins, the vascularity of the thenar and hypothenar eminences, and the flat shape of the hand, allowing a firmer grasp by the snake, are all of importance, determining, as they do, increased rapidity of venom absorption, greater likelihood of intravenous injection, and increased dosage.

Different observers have stated that bites on the fingers are particularly dangerous because the fangs are more likely to be driven deeply into the tissues. This statement is not borne out by the mortality rate of 61 cases of such bites, which was 9.8 per cent., the lowest rate for any location on the upper extremity. This may be readily accounted for by considering the size and shape of the finger, not only making successful local treatment very easy, but tending to decrease the amount of venom injected, because in many cases one or both fangs may fail to penetrate at all, passing harmlessly to the side, or may completely perforate the member.

In connection with the effect of location of the bite on prognosis

the observations of Rinn[60] in his exhaustive thesis entitled, *Le Venin des Viperes Francaises,*" are of interest. Translated, he says: "Considered from the viewpoint of the influence of the location of the bite, our observations give the following results:

Place bitten.	Number cases.	Fatalities.	Percentage mortality.
Fingers	11	1	9.0
Webs between fingers	3	1	33.0
Hand	4	2	50.0
Foot, malcolus and leg	8	3	36.0
Breast, forehead, abdomen	3	3	100.0

"Bites on the fingers are perhaps the most benign because it is very easy to express the venom by suction and pressure."

That the age of the patient would have a marked influence on the mortality might be expected, since the dose of venom per kilo of body weight is of course greater in reverse ratio to the weight of the patient. In Table 6 the mortality in 129 cases of snake bite in children is given. The figures here presented are of very considerable interest, but require no further elucidation.

TABLE 6.—MORTALITY OF 129 CASES IN CHILDREN.

Age of patients.	Number cases.	Number fatal cases.	mortality. Percentage
Children 1 to 5 years, inclusive	23	6	26.0
Children 6 to 10 years, inclusive	36	6	16.6
Children 11 to 15 years, inclusive	51	5	9.8
Children, exact age not given	19	7	36.8
Total number of cases in children	129	24	18.6

A study of the 372 cases in which the sex of the patient is mentioned, with the idea of determining what if any influence sex has on the mortality, has given results which are accounted for with some difficulty. Thus there were 49 fatalities among 277 cases in male patients, representing a mortality of 17.4 per cent., and 10 fatalities among 95 cases in female patients, a mortality of 10.5 per cent. Common sense teaches that resistance to venom intoxications must be approximately equal in the sexes, kilo for kilo of body weight, and this being accepted as true a lower mortality among male patients would naturally be expected. The findings as given must be accounted for on other grounds, therefore, or accepted as tending to show unreliability in all the statistics presented. In my opinion, several factors may reasonably be advanced

60. Rinn, P.: Le venin des vipères françaises, Diss. Faculté de médecine de Nancy, 1905-06, p. 90.

as tending to account for the discrepancy. Thus a fatal termination following bites inflicted by snakes in captivity is very frequent and although a considerable number of such cases are reported only two patients were females, and of these one died. Of the six fatal coral snake cases four patients were males and in two the sex was not stated. The two cases which recovered were males. Finally, it is reasonable to suppose that bites in women would be inflicted more frequently through the clothing, and under such circumstances as regards proximity to civilization, etc., as to render likely the small size of the snake and the availability of appropriate treatment.

The nature of the injection is a factor which plays a most important part in determining the outcome of cases. In the great majority of instances the injection is into the subcutaneous areolar tissues. In a few cases, however, the venom from one or both fangs is discharged directly into the blood stream. Such occurrences, although rarely recognized, are probably partly responsible, as has been pointed out, for the large mortality of bites around the head and neck or on the upper extremity, and such a mode of injection may well have been responsible for some of the very rapid deaths already discussed. In only two cases in the series was there definite evidence pointing towards an intravenous injection of venom. One of these is the case reported by Post[61] and the other is a case mentioned in a personal letter from Dr. John Fitzsimon, of Castroville, Texas. The patient was bitten on the wrist, "on a vein," and died within two hours.

TREATMENT.

A rational and effective treatment of snake bite is to be arrived at only by keeping constantly in mind the clinical nature of the poison, the nature of the pathologic changes induced by it, and the mode of its administration. It may be stated in the beginning that the majority of patients will undoubtedly recover without any treatment, for the simple reason that the amount of venom injected is not a fatal dose. In individuals who have received an amount of venom equalling or exceeding the fatal dose, the rendering of any material aid to the patient is a most difficult matter, requiring very nice judgment and discrimination. In snake poisoning as in many other conditions, the mere length of the list of drugs and other therapeutic procedures recommended as specifics in the treatment of these cases is proof positive of their utter worthlessness in most instances, and a consideration of most of these procedures would be of no interest save for the light it might shed on the

61. See Case 4, Table 2.

ever present tendency of the medical mind to render to its own skill and ability that homage which, all too often, belongs to Nature. Indeed, the list of remedies which have been used in cases of snake bite, includes almost everything conceivable, from Calmette's antivenomous serum to local applications of cloths saturated with urine, or poultices made by splitting open living chickens.

It is customary to take up the consideration of the treatment of snake poisoning under the two general headings of local and general or systemic treatment. Such a classification of the subject is at least open to the criticism that it tends to inculcate the belief that there is a general or systemic treatment, a belief, which so far as the efficacy of any of the means ordinarily employed is concerned, is open to serious doubt. Nevertheless, this division will be followed here, if for no other reason than to emphasize the overwhelming importance of the local treatment. For there can be no doubt that the main therapeutic indication is the prevention of the systemic absorption of a fatal dose of venom from the amount, be it large or small, contained in the tissues immediately around the wound, and if this cannot be met the outlook for the patient, no matter what line of general treatment is employed, becomes exceedingly grave. The limitation and retardation of absorption, by ligatures and other means, and the removal or destruction of the injected venom, are thus the objects of all local treatment.

The absolute prevention of all absorption is probably impossible. Experiments on rats have demonstrated that the animals would die following venom inoculation at the end of the tail, even when this member was amputated within one minute. The control of the circulation in the bitten part, necessary to prevent absorption may be effected by the use of local freezing mixtures or ligatures. Of these the former may be dismissed with brief mention. The ethylchlorid spray has been used and recommended in this country by Crum[22] in conjunction with the use of ligatures and potassium permanganate. Aside from its anesthetic action, I doubt whether it would bring the circulation to a standstill to a sufficient depth to be of much value in cases in which the fangs had penetrated to any great degree and unless kept on hand with an eye to its use in just such emergencies it is a drug which would be rarely obtained under the conditions usually existing where cases of snake bite are most likely to occur. On the other hand, in bites on the head and body, the use of some such procedure is almost the only means at our command. Ligatures, however, are always easily improvised and, since the great majority of bites are on the extremities, easy

of application. Indeed so important are they in the management of these cases, that a detailed consideration of their use becomes necessary.

The amount of good to be gained by the use of ligatures will depend largely on the length of time elapsing between the receipt of the injury and the beginning of treatment. In cases seen early the complete control of the circulation during the preparation for the other local treatment, is certainly indicated. This is best accomplished by the use of a series of ligatures between the bite and the heart, at least one of which should be applied to that segment of the limb containing one bone. The danger of this treatment, if long continued, even with perfectly normal tissues, should be borne in mind, together with the devitalizing local action of crotaline venoms, and the ligatures partially relaxed as soon as practicable. There can be no doubt that many of the cases of extensive local gangrene, following snake bite, should be attributed as much to the prolonged ligation as to the necrotic activity of the venom. In cases seen first after some little time has elapsed, the local swelling being marked and constitutional symptoms already in evidence, complete control of the circulation is of doubtful utility. On the other hand, ligatures so applied as to impede the return flow of blood and lymph, render absorption more gradual, prevent the complete overwhelming of the system by large doses of venom, rapidly absorbed, and yet do not add greatly to the danger of extensive local necrosis. Ligatures applied in this way should replace those completely stopping all circulation, as soon as practicable. It is impossible to lay down fixed rules in regard to the time of beginning the removal of the ligatures and the rapidity with which it should be accomplished; this must be governed by the conditions present in each case. The greatest caution is necessary, however, for in several cases the fatal termination has been attributed to too sudden removal of all impediment to absorption, permitting a large amount of venom to gain access to the general circulation. It is probably safest to begin by intermittently relaxing the ligature nearest the heart, letting it become looser and looser until it is entirely removed. The other ligatures may then be taken off in the same manner.

It is obvious that, having absolutely controled, or at least limited the rapidity of venom absorption by the means just considered, it next becomes necessary to eliminate or destroy as much of the injected venom as possible. Here we may consider separately the various procedures aiming at the absolute removal of the venom, and those aiming at its destruction *in situ*.

Amputation of a bitten limb immediately following the receipt of the injury, or even after a considerable interval if tight ligation had been practiced, would undoubtedly rid the system of the necessity of coping with the larger portion of the injected poison. Such a procedure would be justified and probably often life-saving in those cases in which the whole contents of both poison glands of a large snake have been injected the full depth of the fangs, particularly if the lesion were in the fleshy part of the hand or on the forearm or calf of the leg. Unfortunately it is only under the most exceptional circumstances that any idea as to the amount of venom injected can be obtained. For this reason primary amputation of a large limb will probably be rarely if ever resorted to and I know of no case in which it has been done. On the other hand, the removal of a toe would seem to be entirely justified if it could be done immediately following the injury, or later, if there were reason to suppose most of the injected venom had been confined by ligation. Even in the case of a finger, amputation should certainly be considered under similar circumstances, in any case in which the species or size of the snake or nature of the wound made a guarded prognosis advisable. As has been pointed out previously, bites on the finger are likely to be followed by ankylosis of the joints, contractures of the tendons, or both, resulting in an amount of deformity greatly impairing the usefulness of the member, and little hesitancy should be felt in removing the part if the seriousness of the case seems to demand it.

Immediate amputation having been decided against, the correct surgical treatment of the wound becomes of the utmost importance. Deep excision of the bitten area if sufficiently prompt and radical, probably removes the major portion of the poison. In many locations, however, this treatment is impossible, and cases are seldom seen early enough to render it sufficiently valuable to compensate for its obvious disadvantages. The amount of venom removed by labial suction is probably excessively small, because it is very doubtful if the fang punctures remain patent. Suction following free incision, on the other hand, may be reasonably supposed to facilitate the escape of venom, if the treatment is instituted immediately. Later, after the diffusion of the venom in the tissues, little can be hoped from such a procedure, and the increased danger of infection attending it should contraindicate its employment. The most usual surgical treatment of these cases has been to make two deep incisions through the fang punctures with the idea of allowing the escape of some venom and in order to bring into more intimate contact with the remainder, the drugs used in the attempt at its chemical destruction. As recently pointed out by Martin and Lamb,[7]

ideal treatment requires more than this. The direction of the fang wounds is unknown, the skin may have been pushed or pulled some distance out of its normal position before the fangs penetrated the subcutaneous tissues, or the muscles, when penetrated, may have been in an entirely different position from that present when the wound comes under examination. Because of these facts, the writers mentioned recommend a careful and extensive dissection of the wound. In my opinion, the amount of benefit to be derived from these or any other local measures aiming at allowing the escape of the venom will depend on the degree to which the venom has been taken up by and become diffused through the tissues, which of course will depend on the length of time elapsing before treatment is begun. Most cases of snake bite are first seen by the physician after an hour or more of more or less complete ligation, with the portion of the limb distal to the ligature already considerably swollen and discolored. Under such circumstances, a dissection of the wound, and even free multiple incisions throughout the swollen area, together with such measures as kneading and massaging the part, and its immersion in warm, mild antiseptic solutions, to promote hemorrhage and the escape of serum, offer the greatest likelihood of eliminating most venom. While it is very unlikely that the amount of venom gotten rid of in this manner would be very large, it might, in doubtful cases, be just enough to turn the scale in favor of the patient. In this connection, however, it should be remembered that such radical treatment is not without danger, predisposing as it must to infection, and leaving as an aftermath scars, cicatricial contractures, etc. For these reasons it would hardly be justified in cases in which the size and species of the snake or the location and character of the bite, point towards a favorable prognosis. As stated previously I feel that the rendering of material aid to patients who are really in danger from snake poisoning is a matter requiring the nicest judgment and discrimination which may best be exercised with a thorough understanding of the different points already considered under mortality and prognosis.

In regard to the chemical destruction or neutralization of the venom, it must be emphasized to begin with, that this is only possible in the tissues around the wound, and that it is impossible in any way to affect the venom itself once it passes into the general circulation, save by the use of specific antisera. Obvious as this is from the very nature of the poison, one still reads reports of cases in which various drugs are given hypodermically or by mouth, not as stimulants, but with the idea of acting directly on the venom. Among the drugs which have

the undoubted power to destroy or very materially decrease the toxicity of snake venoms if brought in contact with them in a sufficient degree of concentration, potassium permanganate has attained the most widespread use. The use of this drug has been especially championed by Brunton and Fayer,[62] who recommend that the pure crystals be rubbed into incisions made through the fang punctures. Others use a 1 to 100 solution injected deeply into the tissues around the bite. Most observers believe that the use of potassium permanganate is attended with a diminished mortality. In company with others, however, McFarland[49] has little faith in it, and advocates the hypodermic use of a 10 per cent. fresh watery solution of chlorid of calcium. Solutions of iodin and potassium iodid, of chlorid of gold, and of chromic acid, have all been recommended in this connection. Much that has been said in regard to the abstraction of venom from the tissues will apply with equal force to the use of any of these various chemicals. The question of their efficacy does not hinge on their power favorably to alter the poison, which is unquestioned, but on being able to get them in contact with it in a sufficient degree of concentration. Their use promptly after the bite, preferably through a free dissection of the bitten part, will undoubtedly destroy some of the venom, and by just so much affect the outcome of the case favorably. Their use later, in cases as usually first seen, probably destroys so little of the poison, as to make it a procedure of very doubtful expediency.

In concluding the consideration of the local treatment it is necessary to emphasize the great importance of the application of the principles of aseptic and antiseptic surgery to these cases: The great predisposition to local infection and the important part played by it in causing death, have been already pointed out, and the taking of proper precautions to guard against its occurrence becomes a matter of prime necessity. Once present, infection, or any other local complication, as gangrene, should be treated along general surgical lines. That amputation may occasionally be necessary in these cases, has already been mentioned in considering the complication. A degree of local swelling endangering the vitality of the skin is probably best treated by free incision.

It now remains to be seen how much can be done in the way of aiding the system at large in its effort to overcome the venom absorbed from the local focus. The condition to be treated is essentially a toxemia, and the various symptoms observed are due to the manifold

62. Brunton, Fayer and Rogers: A Method of Preventing Death from Snake-bite, Capable of Common and Easy Practical Application, Proc. Roy. Soc., Lond., 1904, lxxiii, 323; also Indian Med. Gaz., 1904, xxxix, 327.

activities of the various toxic principles contained in the circulating poison. Looking at the matter from a broad general view point the therapeutic indications are perfectly obvious, namely:

1. To destroy the source of the poison.
2. To destroy or neutralize the poison already in the circulation.
3. To aid in and to stimulate its elimination.
4. To support the patient.

All that can be successfully accomplished in the way of eliminating the source of supply of the poison has already been considered; indeed this is the sole object of all the local treatment. The actual destruction or neutralization of the venom already absorbed is, from the very nature of things, impossible save by the use of specific antisera. This ideal treatment will be given the separate consideration which its importance renders necessary. In regard to the general or non-specific treatment, then, there remains to be considered only the means at our disposal to meet the third and fourth indications enumerated above.

So little is known concerning the fate of venom in the body that it is rather difficult to take up intelligently the subject of its elimination. It has been asserted that some of the venom is excreted by the gastric mucosa, and to prevent reabsorption its removal by gastric lavage has been recommended. The experiments made to determine the toxicity of venom administered by mouth indicate so clearly its almost complete harmlessness when taken in this way, that stomach washing would seem to be worse than useless. Whatever poison is excreted in this manner is probably promptly destroyed by the digestive secretions. The kidneys, skin, and bowels should, of course, be kept properly functionating, preferably by a free gratification of the thirst often present, or by the use of physiologic salt solution, which will be considered later.

The general support of the patient during the period of absolute collapse so characteristic of venom intoxication, is of the utmost importance. Here common sense, and a knowledge of the ordinary means used in combating such a condition when due to more frequent causes, will be of greatest value. The patient should of course be kept quiet and warm, in the reclining posture with the head low, and artificial heat applied to the extremities.

Of the long list of stimulants urged on the profession at various times as being of service in this condition, but three need be mentioned specifically. These are alcohol, strychnin, and ammonia. Alcohol, as ordinarily used, is much worse than useless. Reflection on the subject fails to show any ground on which a claim that it is in any sense antidotal to or destructive of snake venom, may be based. When used in

the enormous doses so often referred to in the literature there can be no doubt that alcohol poisoning is added to venom poisoning, and the system taxed just so much the more. More patients have recovered in spite of its use, than because of it. It is well worthy of note of the 78 fatalities in the series of collected cases, four, or over 5 per cent., were attributed by the attending physician to the excessive use of alcohol. In a case reported to me by Dr. Fitzsimon, a boy of three years had been given, before being seen by a physician, over a pint of whisky. The patient died in convulsions. Strychnin has been warmly advocated by Mueller of Australia, and condemned with equal warmth by many observers. It has been used considerably in India and Australia in cases of colubrine poisoning, in which the decided primary depression of the respiratory center would seem to indicate its use, if at all. Nevertheless 113 patients treated with strychnin gave a mortality of 13.2 per cent. and 313 without it a mortality of 4.1 per cent. (Huxtable). Animal experimentation has also shown only bad effects from its use (Noguchi). On theoretical grounds, it would seem to be much less strongly indicated in crotaline than in colubrine poisoning, and its value, and that of ammonia also, in treating the bites of American snakes, may be considered to be decidedly dubious.

In regard to the whole subject of stimulation, it must be remembered that the condition of both circulation and respiration in these cases is, in the main, due to the direct activity of the venom on the vasomotor and to a less degree on the respiratory centers, and that this action, from the beginning, is probably much more than a mere functional depression. What we have to deal with in all probability are definite changes in the make up of the nerve cells; changes of a cytolytic nature which can be demonstrated microscopically when death has not been too rapid. Under these circumstances the writer can see little hope of much benefit to be derived from the exhibitions of stimulants.

The conclusions of Rogers[9] as a result of his study of several viperine venoms, including that of the rattlesnake, have already been mentioned in considering the various toxic actions of venom. Briefly these are that, clinically, the most important toxic activity of rattlesnake venom is its profound lowering of blood pressure, to a point where the weakened respiratory center fails to act and death results, and that this result is due to the direct action of the venom on the vasomotor center, determining a dilatation and engorgement of the portal system. The investigations of Mitchell and Reichert[5] demonstrated the occurrence of this fall of blood pressure in experimental poisoning with rattlesnake, copperhead, and water moccasin venoms.

Nowhere are there experimental findings of more practical importance than in this country, and the simple therapeutic procedures recommended by Rogers as a result of them, are worthy of a thorough trial by those who have cases of crotaline poisoning to treat. For it is obvious that if the circulation can be maintained by increasing blood pressure, the danger of secondary respiratory failure is greatly decreased and the patient may be tided over the crucial point of the disease. The mechanical means advocated in attaining this end, tight bandaging of the limbs and abdominal compression by means of a binder, have not been tried clinically. Menger,[63] however, argued for the use of adrenalin, on theoretical grounds, in 1903; in 1905 he[64] reported a case of water moccasin bite successfully treated by the combined use of potassium permanganate and adrenalin. Hooker[65] has reported a case of rattlesnake bite in a boy of ten years treated with adrenalin and salt solution. The patient made a rapid recovery. Lewis[66] has reported a fatal case of rattlesnake bite in a boy of fourteen years in which adrenalin was used in conjunction with strychnin and ammonia. The well-known action of adrenalin on blood pressure, and the way in which it is brought about, by a direct action on the muscular fibers of the vessel walls, would certainly seem to point to its being of value in these cases, and its administration would at least appear to rest on a much sounder basis than does indiscriminate stimulation with alcohol and strychnin, now so much in vogue.

Another drug, which on theoretical grounds appears to be worthy of an extended trial, is physiologic salt solution. Its use has been advocated by Hooker,[65] who points out that its action is threefold, stimulating the heart, stimulating elimination by the kidneys, and diluting the poison. In severe cases the administration of salt solution by intravenous injection would seem to be strongly indicated and in cases of less severity its use by enteroclysis or hypodermoclysis could, to say the least, do no harm. The solution may be impregnated with oxygen.

Artificial respiration has been found experimentally to be by no means the life-saving process in cases of viperine poisoning which it undoubtedly is in colubrine poisoning (Rogers). In fatal cases of rattlesnake poisoning the circulation usually comes to a standstill

63. Menger, R.: The Rational Treatment of Snake-bite and Others with Adrenalin Chlorid, Texas Med. Jour., Austin, 1902-03, xviii, 445.

64. Menger, R.: Moccasin-Bite Treated with Adrenalin Chlorid Solution, Texas Med. Jour., Austin, 1904-05, xx, 263.

65. Hooker, J. D.: A Case of Snake-Bite Treated with Adrenalin Chlorid Solution, Texas Med. Jour., Austin, 1903-04, xix, 87.

66. See Case 13, Table 2.

before the cessation of respiration.[67] The greater tendency of the ancistrodon venoms, both copperhead and water moccasin, to attack primarily the respiratory center has been pointed out, and in severe poisonings by the bite of either of these snakes, or of a coral snake, artificial respiration might well prove to be life saving. Such was certainly the case in the copperhead poisoning reported by Crum,[22] to which reference has been made, and this means of treatment should certainly be faithfully employed so long as the heart continues to beat.

In concluding the consideration of the treatment of snake poisoning in the United States, there remains to be discussed the use of antisera. It is not my intention to enter at all deeply into this subject, and readers particularly interested are referred to the exhaustive consideration of it by Martin and Lamb.[7] These authors have pointed out that "antivenomous serums are highly, but not strictly specific," which means that in order to attain anything like satisfactory therapeutic results, the antivenomous serum used in combating a case of snake poisoning must have been prepared by using the venom of the particular species of snake inflicting the bite. From this it follows that an antivenomous serum to be of any practical value in the United States must have been obtained from animals immunized against crotaline venoms. No such serum is obtainable commercially. Noguchi has prepared sera with marked antitoxic properties against rattlesnake and moccasin venoms, but only on an experimental scale. It is obvious, then, that such a thing as the serum treatment of snake poisoning, so far as this country is concerned, simply does not exist.

Nor is it likely that it ever will. The difficulties in obtaining a sufficiently large supply of venom to render possible the production on a commercial scale, of an antivenene, could only be obviated by breeding large numbers of snakes in captivity, and even with a large and continuous supply of venoms there would still remain to be overcome the difficulties pointed out by McFarland,[40] the severe local reaction and likelihood of infection in the animals used. Having succeeded in overcoming all these difficulties the value of a serum so prepared even if it could be made polyvalent, i.e., protective against all of the three pit viper venoms, would be dubious, unless it could be made more potent than Calmette's serum. As pointed out by Martin and Lamb[7] this serum in doses of 1 c.c. protects a guinea-pig against only 10 minimum lethal doses of the cobra venom while the same amount of diphtheria antitoxin protects against 100,000 minimum lethal doses of the toxin, and an equal amount of tetanus antitoxin against 200,000 minimum

67. See Case 10, Table 2.

lethal doses of the tetanus toxin. It is doubtful, finally, if the morbidity and mortality from snake bite in the United States will ever demand the preparation of an effective antivenomous serum. Such reasoning, however, certainly does not apply to India, with an annual number of deaths from this cause amounting to about 20,000.

GENERAL SUMMARY AND CONCLUSION.

I wish to lay special stress and emphasis on the following points which I hope have been brought out in this article:

1. Technically speaking it is correct to say that there are over twenty species of poisonous snakes found in the United States, but it is decidedly less misleading, at least from the view-point of the physician and therefore in medical literature, to place the number at four, the coral snake, the rattlesnakes, the copperhead, and the southern water moccasin, qualifying this with the statement that two species of coral snakes and several of rattlesnakes are recognized by herpetologists.

2. These snakes are all found together only in the group of states roughly indicated as extending from mid Texas to the Carolinas, inclusive, the remainder of the country harboring at most not more than two of the four mentioned.

3. The presence of a pit between the eye and nostril, on the side of the face, or of undivided ventral scales on the tail immediately stamp a snake as dangerous, and the absence of these points indicates the harmless character of any snake in the United States, with the single exception of the gaudily colored coral snakes, confined entirely to the southern states.

4. While it is impossible to state the morbidity from snake bite in the United States, it is undoubtedly excessively small, and over 99 per cent. of it is due to the crotaline snakes, or pit vipers.

5. The most important complications of snake bite are sepsis and acute alcoholism, probably respectively responsible for about 10 per cent. and 5 per cent. of the fatalities.

6. The mortality of all cases is 10 per cent., that from the different species being as follows: Coral snakes, probably from 25 to 50 per cent.; water moccasins, 17 per cent.; large species of rattlesnakes, 11 or 12 per cent.; copperhead and ground rattlers, *nil* in uncomplicated cases in adults up to about 5 per cent. when all cases are included.

7. Bites on the head and trunk are much more dangerous than those on the extremities, and those on the upper extremity at least twice as dangerous as those on the lower.

8. The mortality in children under ten years of age is at least double that in adults.

9. The local treatment, having for its object the limiting of venom absorption, is of the greatest importance; in order to be effective it must be both prompt and radical; in all surgical procedures around the wound, special precautions must be taken against infection.

10. The ideal constitutional treatment by means of antisera is now absolutely impracticable and, therefore, little can be done other than keeping the patient quiet and warm; the administration of adrenalin and salt solution; the use of such mechanical means as bandaging, abdominal compression, and posture to keep up the blood pressure and circulation in the vital centers; and the institution of artificial respiration when indicated.

In conclusion I wish to express my keen appreciation of the kindness of those physicians and others too numerous to mention who have aided me in my endeavor to collect a sufficiently large number of cases to make the statistics based thereon of some value. It is a very keen pleasure to me to make the following specific acknowledgments: To Dr. George Tully Vaughan and Dr. George M. Kober for most valuable advice and encouragement. To Dr. I. W. Blackburn for his great kindness in superintending the making of, and for retouching, the negatives of Figures 5 and 6; the great clearness and accuracy of these figures is due entirely to Dr. Blackburn, and to Mr. Keefer, the photographer at the Government Hospital for the Insane, Washington, D. C. To Dr. William Hough for aid in making the dissections shown in Figures 5 and 6. And finally to the authorities of the U. S. National Museum, for the negative used in Figure 4, for the permission to make use of Figures 1 and 2, and for the specimen of *Crotalus adamanteus* used in making the dissections mentioned.

Twentieth Street and Florida Avenue.

THE NATURE OF SHOCK.*

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In the clinical literature, shock designates a group of grave symptoms which frequently lead to the death of the individual. At the post-mortem examination no anatomic changes can be detected which would account for death and the grave symptoms preceding it. The fatal disturbance underlying the phenomenon of shock is, then, exclusively of a functional nature. From a purely scientific point of view, shock is, therefore, a subject pre-eminently belonging to the domain of pathologic physiology. It should be mentioned that the term shock employed in normal physiology is not identical with the syndrome in which we are interested here. The shock of the physiologists refers to the depression and suppression of spinal reflexes brought about by a direct injury to the cord. We shall not stop here to discuss the possibility of a common ground for both forms of shock. We wish, on the contrary, to point out one strikingly distinguishing feature: physiologic shock is practically not progressive; on the contrary, as a rule, it is fairly rapidly regressive. Clinical shock is, as a rule, progressive, although, as we shall see, it is not invariably fatal.

In selecting the discussion of the nature of clinical shock as the subject of my present address, it is chiefly my intention to record some experimental facts which we obtained in the course of various series of investigations and which may have some bearing on the interpretation of clinical shock.

As an introduction to this report, however, it will be necessary to dwell briefly on the clinical facts of our syndrome and also to review briefly the theories as to the nature of shock now in vogue and the experimental facts on which they are based. As to the clinical picture of shock I could not do better than to quote the description of a concrete case of shock as lucidly given by Fischer[1] nearly forty years ago:

> A strong and perfectly healthy young man was struck in the abdomen by the pole of a carriage drawn by runaway horses. No recognizable injury was done to any of the internal organs. Nevertheless, grave symptoms made their appearance immediately after the accident. The injured man was lying perfectly quiet and paid no attention to anything going on around him. His face was drawn and

* Address delivered at the Academy of Medicine of Toronto, April 7, 1908.

1. Fischer, H.: Samml. klin. Vortr., 1870, No. 10, p. 119.

peculiarly elongated, the forehead wrinkled and the nostrils dilated. His weary, lustreless eyes were deeply sunk in their sockets, half covered by the drooping eyelids and surrounded by broad rings. The pupils were dilated and reacted sluggishly to light. The eyes had a glassy and vacant expression. The skin and the visible mucous membranes had a marblelike pallor. Large drops of sweat hung on forehead and eyebrows. The rectal temperature was subnormal. The sensibility of the entire body was greatly reduced; the patient reacted slightly and only to very painful impressions. No spontaneous movements of any sort were made by the patient. On repeated and urgent requests he showed that he could execute limited, brief movements with his extremities. When the limbs were lifted passively and then let go, they fell down like dead. The sphincters were intact. The urine obtained by catheter was scanty and concentrated, but otherwise normal. The almost imperceptible pulse was rapid, irregular and unequal. The arteries were narrow and of very low tension. The patient answered slowly, reluctantly, and only after repeated urgent questioning. His voice was hoarse and weak, but well articulated. On being repeatedly questioned, the patient complained of cold, faintness and deadness of all parts of the body. When he shut his eyes he felt nauseated and dizzy. The respirations appeared irregular; long, abnormally deep, sighing inspirations interchanged with rapid and superficial ones, which were scarcely visible or audible.

Recapitulating briefly, the essential symptoms of this typical case of traumatic shock consisted of general profound apathy, reduced sensibility, extreme motor weakness, great pallor, very rapid, small pulse, thready and soft arteries, irregular gasping respirations and subnormal temperature.

Fischer does not state the subsequent fate of that patient.

Shock brought on by a blow on the abdomen has often had a rapidly fatal termination. This is graphically illustrated by the following instances given by Sir Astley Cooper:[2]

A man walking through Fleet street (London) one day, happened to quarrel with a woman, when another man came up and gave him a blow in the region of the stomach, which caused almost instantaneous death. On dissection, no cause could be found to account for his sudden death.

A man belonging to the India House was attempting to lift a weight, when another came up and jocosely said, "Here, stand on one side and let an able man attempt it," and at the same time gave him a slight blow on the stomach, when the poor fellow dropped down and expired. His body, on being opened, showed no marks of violence.

Similar rapid fatal terminations from shock are reported from injuries to the testicles. John Hunter[3] is stated to "have seen a man die almost immediately on the loss of a testicle." Fischer[4] tells that he has seen a strong man dying of shock a few hours after he was bitten in the testicle by a wild horse. However, there are some cases with all the symptoms of profound shock which, nevertheless, recover completely.

2. Cooper, Sir Astley: Lectures on Surgery, 1830, p. 9.
3. Hunter, John, quoted by Morris: Shock, London, 1867, p. 13.
4. Fischer, H.: Samml. klin. Vortr., 1890, No. 10, p. 119.

Travers,[5] who probably was the first surgical author to use the term shock with the precise meaning attached to it now, writes:

> Again and again I have left the bedside of patients brought into the hospital pulseless and apparently moribund without any external injury, having suffered falls or blows so serious as to have induced the symptoms of prostration to an alarming extent, and have found them on the succeeding day, to my great surprise, restored to the tone and tranquility of normal health.

The shock described in the foregoing instances is generally designated as traumatic shock. It is characterized by sudden onset and rapid development of the symptoms following immediately on an injury more or less violently and rapidly executed. In recent literature we frequently meet with the term "surgical shock," which has reference to the condition of shock which develops in the course of a surgical operation or soon after it. It occurs most frequently in abdominal and brain operations. It differs from traumatic shock only in its slower development, although most of the recent writers have dwelt in their description specially on the behavior of the heart and the blood pressure. Possibly the pathologic state preceding the operation, the anesthesia and the loss of blood combine to obscure the sharp outlines of shock as seen in purely traumatic cases.

As to the theories, the earlier writers spoke in a vague way of the central nervous system as being the seat of the affection. Cases of shock produced by mental terror without any physical injury gave support to such a view. It was assumed that a strong emotion, as well as a physical commotion, caused some sort of profound molecular changes in the brain.

The first well-defined theory was brought forward by Fischer,[6] who founded it on the well-known experiments of Goltz. Repeated strokes on the abdomen of a frog causes stand-still of the heart and paralysis of the arteries and the veins of the abdominal cavity, which is brought about by reflex paths. Fischer assumed then that traumatic shock consists of a vasomotor paralysis, especially of the splanchnic area, where the bulk of the body's blood is accumulated, with a consequent anemia in other parts. Shock was a hemorrhage into the body's own large veins. According to Fischer, the vascular disturbance was the primary cause, all other symptoms were secondary phenomena due to the consequent anemia of the peripheral parts.

Another theory was that of Groeningen,[7] who assumed that all the nerve centers were equally affected, not by paralysis, but by exhaustion

5. Travers: Inquiry Concerning Constitutional Irritation, London, 1827.
6. Fischer H.: Samml. klin. Vortr., 1890, No. 10, p. 119.
7. Groeningen, quoted by Warren: Surgical Pathology.

brought on by the traumatic over-stimulation. Mansell Moullin is credited by Warren[8] with the theory that the various nerve centers of the body were not exhausted, but inhibited.

These and some other theories were simply construed at the writing desk of their authors. It is only within the last decade that more or less efficient attempts were made to study the nature of shock by the experimental method. As far as I can see, the experimentation led up only to a study of surgical shock; that is, to a shock which developed gradually, similar to that occurring in surgical practice, and there are no reports of experiments in which shock developed as rapidly as in the traumatic cases.

The most extensive series of experimental work on the problem of shock was carried out by George W. Crile. The protocols of the experiments and the conclusions drawn from them are published in two large monographs.[9] The experiments were made on dogs while under ether anesthesia. The various tissues, like skin, muscle, nerve, bone, etc., in the various parts of the body: head, neck, thorax, abdomen, extremities, etc., were subjected to various strong mechanical irritations, to burning and to electric stimulations, with a view to study their effects on blood pressure and on the production of shock. The effects of these various stimulations on respiration and cardiac activity were also studied but less extensively. The chief facts reported by Crile are as follows:

Strong irritations, like cutting, tearing, burning the skin all over the body, except over the abdomen and testicles, and of the sensory nerve trunks cause, as a rule, a more or less strong rise of blood pressure during the stimulation. Cutting the skin over the abdomen or over the testicles causes as a rule a fall of blood pressure. Opening the abdomen, exposing and handling the intestines, cause a continuous fall. Repeated stimulation of the skin or nerve trunks leads at first to a diminution in the increase in the rising effect, then comes a stage in which the stimulation causes primarily a fall and finally ends up with a stage in which stimulation has no effect whatsoever on the blood pressure. At that stage usually the blood pressure is very low and can not be permanently improved by any medicinal or other treatment. This is, according to Crile, the stage of complete surgical shock. The development of shock is hastened by the strength of the repeated stimuli and by the amount of tissue involved in the stimulation; under all circumstances, however, its development is always a slow and gradual one.

The characteristic signs of surgical shock are, according to Crile, the very low blood pressure and the impossibility of influencing the pressure by any stimulation. The cause of it is exhaustion, the breakdown of the vasomotor center by the preceding over-stimulation. Adrenalin may

8. Warren, John Collins: Surgical Pathology, 2d ed., 1900.

9. Crile, George W.: An Experimental Inquiry into Surgical Shock, Philadelphia, 1899; also Blood Pressure in Surgery, Philadelphia and London, 1903.

temporarily raise the blood pressure by a contraction of the muscles of the wall of the blood vessels; also transfusion or peripheral mechanical pressure may raise the blood pressure simply by hydraulic principles, but the rise will be only temporary. The pressure will not be self-sustaining on account of the complete exhaustion of the vasomotor center.

According to Crile, then, failure of blood pressure is the primary and sole cause of all the symptoms of shock, and this failure has as its cause solely the exhaustion of the vasomotor center. The cardiac and respiratory failures and other phenomena are only secondary consequences or subsidiary factors to the primary cause, the exhaustion of the vasomotor center.

Crile makes a distinction between shock and collapse. In the latter low blood pressure and all the other symptoms of shock may be present. But the onset of collapse, Crile says, is sudden and the conditions are amenable to stimulation because the vasomotor center is not exhausted, but only depressed and can be raised to activity by stimulation. As far as I can see, the difference between shock and collapse, according to Crile, is as follows:

> The onset is gradual in shock and sudden in collapse. Collapse may have its origin in cardiac, respiratory or vasomotor insufficiencies; shock is of vasomotor origin only. Collapse is amenable to stimulants and stimulation; shock is not. In shock the vasomotor center is exhausted; in collapse, if this center is affected, it is only functionally depressed.

I shall not discuss here whether it may be possible to distinguish at the bedside of a human patient between shock and collapse, although such a distinction might be of practical vital importance, since, according to Crile, stimulants like strychnin or alcohol may hasten the end in shock, but may save life in collapse. I wish only to call attention to the fact that shock as described by Crile fits only surgical shock, and that traumatic shock, especially as was described classically by earlier writers, had, on the contrary, mostly, if not always, a sudden onset. I hardly think that Crile assumes that all these cases were only of the collapse variety. But I could not find in his writings a discussion of this apparent discrepancy.

Crile's results and teachings have been widely accepted in the surgical world, especially in the United States and England. They were endorsed by such prominent experimental surgeons as Victor Horsley and Harvey Cushing. They were given a wide prominence by the lectures of Mummery[10] in England and they have found their way into all new text-books.

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10. Mummery, P. Lockhart: Lancet, 1905, i, p. 696, ff.

Within the last few years, however, some divergent views made their appearance. Boise,[11] in the United States, and Malcolm,[12] in England, who are willing to accept the facts as they are reported by Crile, attempted to interpret them differently. They believe that the low blood pressure and the venous stasis observed in surgical shock need not be due to paralysis of the blood vessels and an exhaustion of the vasomotor center, but, on the contrary, can be and are the outcome of a high stimulation of the center and a strong contraction of the heart and the arteries. The theories of these writers are not supported by any observations or experimental tests of any weight, and we shall not enter into a discussion of the validity of their theoretical arguments.

I shall mention particularly, however, some important experimental work recently done by very competent physiologic investigators. W. H. Howell[13] undertook to produce shock in anesthetized dogs either by prolonged handling of the intestines or by applying heat to a large surface of the skin or by operations on the brain. He was frequently confronted with the experience that what produced shock readily in one animal singularly failed to have any effect on another animal. Howell distinguished two forms of shock, cardiac and vascular. In some cases the pulse would be feeble and very rapid, while the blood pressure would remain of a fairly good height. In other animals the blood pressure would drop to forty or twenty millimeters of mercury, while the pulse would also be greatly accelerated. Cardiac shock could occur without vascular depression, while vascular shock was always accompanied by cardiac shock. Howell thinks that neither the vascular nor cardiac shock was due to an exhaustion of the medullary centers, for in neither case were there any signs of a preceding over-excitation. He assumes that both cases of shock are due to an inhibition of the centers in the medulla, that is, an inhibition of the tonus of the vagus center which causes acceleration of the heart and an inhibition of the vasomotor center which leads to vascular shock.

Howell, then, like Crile, sees in the disturbance of the circulation the essential characteristic of shock, but differs from him in that he does not assume that the vasomotor center is exhausted and that he lets the cardio-inhibitory center share in the causation of the shock.

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11. Boise: Amer. Jour. Obstet., 1907, lv, p. 1.
12. Malcolm: Lancet, Aug. 26, 1905, ii; also Lancet, 1907, i. p. 497.
13. Howell, W. H.: Contributions to Medical Research, dedicated to Victor C. Vaughan, 1903.

The vasomotor studies of W. T. Porter alone and with his pupils[14] led him to results and views entirely antagonistic to those brought forward by Crile. In the first place, in disagreement with Crile, he states that in his numerous experiments he failed to find an instance in which stimulation of an afferent nerve caused a significant fall of blood pressure, except, of course, on stimulation of a depressor nerve. In his experiments, crushing or electric stimulation of the testis always gave a rise and not a fall of the blood pressure. Continuous stimulation of the central ends of the sciatic, brachial or other afferent nerves for many hours gave uniformly the same rise of pressure as at the beginning. An analysis of 765 blood pressure records from stimulations of the sciatic and brachial (and depressor) nerves of rabbits, cats and dogs brought out the result that the "percentage change in blood pressure, which is the true index of the condition of the vasomotor cells, increases as the blood pressure falls." Even in experiments where all the clinical signs of shock were present: the blood pressure very low, the temperature subnormal, the heart beat weak and often irregular, and the irritability of the nervous system apparently much reduced, stimulation of the depressor nerve lowered the blood pressure by 45 per cent. All these data, says Porter, are wholly opposed to the hypothesis that exhaustion of the vasomotor center brought on by over-stimulation can be the cause of surgical shock. Porter offers no theory of his own as to the nature of shock, but he is very emphatic in his assertion that the vasomotor cells in shock are neither exhausted, depressed nor inhibited. Porter contradicts Crile's facts and disagrees with his exhaustion theory; but apparently he also disagrees with Howell's views, that inhibition of the vasomotor and cardiac centers are at the bottom of the phenomena of shock.

In connection with this review it may be mentioned that, according to a recent statement of Sollmann[15] and his associates, "corrosion or violent irritation of the gastric mucosa, submucosa and serosa, or of the parietal peritoneum has generally no effect on blood pressure or respiration in anesthetized dogs, the observations extending some time over an hour."

This brief review will suffice to show that the experimental era has not yet solved the mystery of shock, and that the bringing forward of new experimental facts capable of shedding some more light on our puzzling problem is not yet a superfluous luxury. Before beginning the report of our own experimental results I wish to complete the foregoing review by the addition of two brief statements.

14. Porter, W. T.: Am. Jour. Physiol., 1907-'08, xx, pp. 399, 444 and 500.
15. Sollman, Brown and Williams: Am. Jour. Physiol., 1907, xx, p. 74.

Henderson[16] has recently adopted Mosso's theory of acapnia also for the causation of shock. Acapnia means an insufficiency of carbon dioxid in the tissues and fluids of the body, and Mosso believes that this insufficiency is the cause of mountain disease. Henderson believes that the lack of carbon dioxid is also the cause of shock which, for instance, develops in laparotomies on account of the escape of this gas from the exposed peritoneum and intestines.

The other statement has reference to the brief mention of Bainbridge and Parkinson[17] last year of two autopsies of postoperative shock in which the chromaffine tissue of the suprarenals was absent. If such findings should turn out to be the rule, we may soon find a new and plausible theory of the nature of shock. This, however, must be left to the future.

Our experiments which I wish to mention here were not undertaken and carried out with a view of determining the nature of shock. Laparotomies were made on animals under various conditions for the purpose of studying certain problems in connection with the gastrointestinal canal. In these studies, however, some facts came to light which may be of assistance in the elucidation of some of the mysteries of shock, and that is the reason why I wish to report them here.

The first series of experiments deals with the motility of the gastrointestinal canal. We found there the fact that simple opening of the abdomen has a profound influence on this motility. Experimenters open the abdomen as one opens the door of a room to see the doings and hear the conversation which is going on, and they are then surprised that everything is quiet. If the abdomen of a rabbit is open it is found that the bulky organs, the stomach and cecum, which fill up nearly the entire abdominal cavity, are practically without any motion.

The literature, therefore, contains hardly any statement concerning the motility of these organs, especially that of the cecum, which is very large in the rabbit. Dr. Auer and myself[18] have discovered, however, that if a normal rabbit is stretched out on its back and the hair over the abdomen cut the regular movements of the stomach and cecum are very plainly visible; the movements of the cecum are especially coarse and easily visible and palpable. Nevertheless, on opening the abdomen there is not a sign of these movements, which appear to be suppressed by this procedure.

16. Henderson, Yandell: Am. Jour. Physiol., 1908, xxi, p. 126.

17. Bainbridge and Parkinson: Lancet, 1907, i, p. 1269.

18. Meltzer and Auer: Zentralbl. f. Physiol., 1907, xxi, No. 3; Proc. Soc. for Exper. Biol. and Med., 1907, iv, p. 37; also John Auer: Am. Jour. Physiol., 1907, xviii, p. 347.

We then carried out a series of experiments to find out the cause and nature of this suppression. The cecum was studied first. In the beginning we sought to determine whether it is not the pain due to the incision after the animal comes out from the anesthesia which inhibits the movements. For this purpose we have first sectioned the spinal cord at the upper end of the dorsal region. Sooner or later the movements of the cecum were as regular as usual. We could now open the abdomen without causing the animal any pain. But it was found that now, too, there was not a sign of cecal movement. The suppression, then, was not caused by pain. The opening of the abdomen admits air, and sometimes cold air, and it is usually assumed that this has a profound effect on the peritoneum and intestines. We thought that this might be the cause of the suppression of the movements. In testing this surmise we discovered that it was not necessary to open the abdomen; simple free dissection of the skin of the abdomen from the underlying muscles was sufficient to stop these movements. It was then evident that the suppression of the movements was not due to direct action upon the cecum but to some reflex act. Temporary closing of the skin over the wound restored the movements again. That it was not the contact of the skin area with the cold air, or at least that it was not this alone, which caused reflexly the suppression of the movements could be proved by the fact that covering the area with warm physiologic solutions did not restore the movements. A similar result was obtained, though the effect was less strong, when the skin of the thighs was freely dissected. Furthermore, even submerging the posterior part of the animal with the cut cord in a bath of 40 degrees C. stopped the cecal movements for some time. Apparently any adequate stimulus applied to the animal caused by way of reflex to the spinal cord an inhibition of the cecal movements. The dissection of the skin presents such a stimulus, and although we are as yet ignorant as to which of the factors accompanying the dissection is the essential stimulus, we know that the dissection presents a group of abnormal conditions, and any abnormal condition might serve as a stimulus. The assumption that the suppression of the cecal peristalsis is an act of reflex inhibition we have further tested by the complete destruction of the spinal cord. In this case dissection of the skin was incapable of interfering with the cecal peristalsis, which was then even better than before. The evil ghosts of exhaustion and fatigue which for more than half a century cast their dark shadows on many bright ventures in physiology could not obscure the issue here. The suppression of cecal peristalsis by dissection of the skin could not have been brought on by overstimulation and exhaustion, since after destruction of the cord and

dissection of the skin the peristalsis was not hampered and in fact was better than before. The mechanism of this reflex inhibition of peristalsis is apparently this. The splanchnic nerves and perhaps also some hypogastric nerve fibers are inhibitory nerves for the gastrointestinal canal, just as the vagus is an inhibitory nerve for the heart. In the normal state an inhibitory tonus is present, that is, cutting of the splanchnic nerves causes an increase of the normal peristalsis. The tonus is probably sustained by continuous mild reflex stimulation from the periphery. When an abnormal, strong stimulus is applied to the periphery, like the dissection of the skin, reflex inhibition becomes increased to such a degree as to completely stop the normal peristalsis. When, however, the cord is destroyed and no spinal reflexes are possible, the dissection has no effect and by the elimination of the normal tonus the normal peristalsis becomes even greater.

Our further experimentation, however, revealed the presence of another inhibitory mechanism. We found that after destruction of the cord there was a sharp difference in the effect between simple dissection of the skin and complete opening of the abdomen. In the latter case the peristalsis, which now did not disappear immediately after the performance of the laparotomy, was not as complete as normally and continued only for a short time. Even in a warm bath of a physiologic solution the cecal peristalsis ceased after ten or fifteen minutes. Since there could be no reflex effect, the early subsidence of the movements must have been accomplished by the stimulation of some peripheral inhibitory mechanism. We did not try to locate the habitat of this mechanism, whether it be in the peripheral ganglia, nerve endings or within the muscle cells of the intestines.

This series of experiments, then, established safely the following conclusions: That simple dissection of the skin over the abdomen presents a distinct stimulus; that this stimulus when the corresponding part of the spinal cord is intact causes a reflex of an undoubted inhibitory character; when the cord is destroyed the opening of the abdomen brings on a stimulation of peripheral inhibitory mechanisms and that, therefore, when the cord is intact the opening of the abdomen is instrumental in bringing out a two-fold inhibition—a reflex inhibition and an inhibition of a local peripheral mechanism.

These conclusions found their verification in results at which Cannon and Murphy[19] arrived in a series of different experiments. Cannon, as is well known, studies the movements of the gastrointestinal canal in

19. Cannon and Murphy: Jour. Am. Med. Assn., 1907, xlix, p. 840.

normal animals by the fluoroscopic method. In a series of experiments which he carried out together with F. T. Murphy it was found that crushing the testes of cats under anesthesia stops the peristaltic movements of the small intestines. When the splanchnic nerves were previously cut, however, the crushing of the testes did not interfere with the movements of the intestines. This shows that the crushing of the testes presents a stimulus which causes reflex inhibition of the intestinal peristalsis. Furthermore, Cannon and Murphy found that the transportation of food from the stomach through the intestines, which in cats does not stop by simple exposure of the intestines to the air, is greatly inhibited when the intestines are handled within the abdominal cavity and still more so when they are removed outside of the cavity and handled there. To test the nature of this inhibition Cannon and Murphy repeated these experiments in animals whose splanchnic nerves were previously cut. It was found that the handling still inhibits the movements. The inhibition called forth by the handling, therefore, is due to some local mechanism. Here again we have two varieties of inhibition —reflex inhibition and local inhibition of peripheral origin.

Before discussing the bearing of these facts upon the question of the nature of shock we shall first record some other observations brought to light by the investigations of Dr. Kast and myself in a series of experimental studies of the sensibility of the gastro-intestinal canal.

As is now well known, the observations made in human laparotomies under local anesthesia led the surgeons to the view that the abdominal viscera feel no pain and possess no sensory nerve fibers. In an extensive study which we made on dogs we found that the intestines are sensitive enough as long as they remain within the abdominal cavity and are very little or not at all exposed to the air. When the abdomen is freely opened and the intestines removed from the cavity the sensibility becomes greatly reduced or entirely abolished temporarily or even permanently. It is with sensibility the same as with motility; the sudden opening of the abdomen is like the sudden opening of a door which throws a hush on the lively company inside of the room. When the abdomen was opened under anesthesia and one loop of intestine was gently fixed between the branches of a dressing forceps and the abdomen then closed with temporary sutures, any moderate pressure on the protruding handle of the forceps invariably called forth an unmistakable sign of the sensation of pain. The result would remain constant for hours. If, however, all the temporary sutures were opened at once and stomach and intestines permitted to escape from the abdominal cavity,

in a minute or two the sensations of the intestines would be greatly reduced or completely abolished and would remain so for a shorter or longer period until the intestines were returned to the abdominal cavity and the abdomen closed or at least kept well covered with warm physiologic solution. We shall not enter here, of course, into any details of these experiments. We wish, however, to call attention to the following accompanying circumstances. Simultaneously with the loss of intestinal sensibility a distinct reduction of the sensitiveness of the skin over the entire body takes place, and at the same time the animal becomes distinctly apathetic. The dog, which a few minutes before was whining and restless, suddenly becomes perfectly quiet and strikingly indifferent, although the eyes are wide open and the lid reflex is active. A strong stimulus applied to the skin would wake up the animal, but only to sink again into the lethargic condition. The intestinal and skin insensibility and the general apathy set in even if the opening of the abdomen occurred in a warm bath of saline or Ringer's solution. The reduction of the sensibility of the skin is as a rule less pronounced than that of the intestines; the sensitiveness of the skin returns also a good deal sooner. The general apathy lasts a good deal longer. During all this time the blood pressure remains high; it may be as high as 150 millimeters of mercury or even higher. The pulse, which sometimes becomes rapid for a short time, soon returns to normal, and the respiration may be even slower than normally.

What does this loss of sensibility and apathy mean? With high pressure the phenomena can not be due to anemia, and with normal pulse, normal pressure and normal respiration it does not look like an exhaustion. Knowing now that the suppression of the motor phenomena by the opening of the abdomen is surely an inhibitory effect, we assume that the blunting of sensation and perception also means an inhibition, that is, an inhibition of the receptive sensory elements. Furthermore, since the processes of the reduction of the sensation from the skin and of the general apathy can take place only within the central organ, we have reason to assume that the stimulating factors combined with the opening of the abdomen create at the central end of the sensory nerves inhibitory processes which are responsible for the phenomena above described.

For reasons, into a discussion of which we do not wish to enter here, we consider it possible that in the nerve fibers of the intestines the peripheral receptive endings might also become somewhat affected by the opening of the abdomen. At any rate, the sensitiveness of the intes-

tines was distinctly more reduced than that of the trunks of the mesenteric nerves.

We may mention here an observation made by Dr. Auer and myself in studies upon the respiratory vagus. Although these studies are far from complete, the one fact which interests us here stands out quite clearly. It has been known for half a century that stimulation of the central end of a vagus nerve, especially in rabbits, affects the respiration so as to cause a standstill. Numerous investigations were made on this subject and there has been a contention among the various writers whether the standstill occurs in inspiration or in expiration. Standstill in inspiration means a tetanic contraction of the diaphragm, and standstill in expiration means an inhibition of the spontaneous contractions of the diaphragm. The inhibition occurs within the medulla oblongata and is of the same nature as the inhibition produced by the stimulation of the central end of the superior laryngeal nerve. Some years ago I[20] showed that both statements are true, namely, that in some animals stimulation of the vagus causes standstill in inspiration, in others standstill in expiration. This means that the vagus contains two kinds of nerve fibers—stimulation of one kind causes excitation, that is, inspiration, and stimulation of the other causes inhibition of inspiration. Which of the effects prevails depends in each particular case upon conditions which are as yet unknown to us. We have now observed in a few dogs and rabbits that after the abdomen is widely opened stimulation of the central end of the vagus causes invariably an inhibition of inspiration. This means that the opening of the abdomen contains elements which favor the predominance within the medulla of an inhibitory state for the respiration. We may add that in these experiments, too, it was evident that the opening of the abdomen is the cause of a manifest reduction of the sensibility of the skin.

Turning again to our experiments on the sensibility of the abdominal organs, we have to point out a few more facts which are of special interest to our problem. In many of our dogs, especially in vigorous animals, blood pressure, pulse and respiration would remain normal for many hours, in fact the experiment had to be broken off before there was any sign of a so-called vascular shock. Meanwhile the viscera had been repeatedly eventrated and replaced in the abdominal cavity, the animal becoming more and more insensible to any stimulation and deeply apathetic while the blood pressure never was less than at least 100 millimeters mercury. In other animals the blood pressure dropped

20. Meltzer: Arch. f. Physiol., 1892, p. 340.

within two or three hours to 60 or 50 millimeters, the pulse ran up to about 180, the respiration was irregular and otherwise the animal presented the picture of deep shock. Again, in another comparatively small group of animals it came to pass that immediately after a sudden release of the temporary ligatures of the abdomen the animal sank into a state of deep shock. It lay absolutely motionless as if paralyzed; no manner of stimulation of the skin would bring out any reaction; the eyes were half closed with a completely indifferent look, though the lid reflex was not entirely abolished. The respiration was very slow and gasping, the pulse very rapid and small, although the blood pressure was still 70 or 60. The mucous membranes were usually pale, the viscera showing at least no hyperemia. The blood was always dark. All this would occur even when the opening of the abdomen took place in a bath of 40 degrees C. The animals of this group were far from vigorous, of a meek temperament and not well nourished. Even these animals did not die spontaneously; they were usually killed by clamping the trachea or by putting the tracheotomy tube under water, and the remarkable fact was then noted that in these animals the asphyxia did not result in any convulsions.

The shock seen in these few animals had a remarkable similarity to traumatic shock as described by Fischer and others in the human being, although in two of these animals the blood pressure was not lower than 60 millimeters.

From this series of experiments we have learned the following facts which have a bearing upon our problem. In all experiments in which our attention has been directed toward this point, opening of the abdomen and evisceration led invariably to a reduction of the sensibility of the skin and to general apathy, from both of which the animal is apt to recover sooner or later when the viscera are properly taken care of. While both of these conditions may attain sometimes a considerable degree of intensity, the heart and blood pressure may remain entirely unaffected. If the tough handling of the abdominal viscera continues, the insensibility and the general apathy increase. In vigorous animals this did not readily lead to a surrender of the functions of the body to complete shock, so that even after many hours of exposure and handling, blood pressure, heart and respiration still had suffered little. In less vigorous animals also the last named functions gradually surrendered to the effects of continuous rough handling of the viscera; these animals gradually sank into complete shock. Finally in animals with reduced bodily resistance complete shock appeared soon after laparotomy and evisceration.

In some cases an undoubted profound shock was present, although the blood pressure was not lower than 70 or 60 millimeters, a degree of pressure which, if not complicated by any other ill conditions, is still far away from the danger line.

We wish to point out especially that in our experiments in the cases in which the development of shock was gradual the symptoms of insensibility, general apathy and complete muscular relaxation invariably made their appearance long before the onset of cardiac and vascular breakdown.

Before continuing the discussion of our experiments further, I wish to make the following remark with reference to the symptoms of shock. In the above reported recent literature on shock low blood pressure is the paramount symptom, possibly also a rapid pulse. In the lucid description of traumatic shock of some of the older writers blood pressure was represented only by the few words that the arteries were of low tension, while there was a great deal to say about the peculiar mental state, the insensibility, the immobility, the respiration, etc. I may also mention here that in referring to Goltz's experiments on the effects of stroking the abdomen of frogs, usually only the condition of the heart and blood vessels is taken into consideration, while Goltz has expressly pointed out that as long as the animal is under the influence of the stroke reflex it is as if paralyzed and seems to be without sensation. Painting the leg with acid causes no reaction; later, when the animal recovers, it tries to get rid of the irritant. I emphasize these points to show that the symptoms of general apathy, of insensibility and of muscular weakness are integral symptoms of shock. The recent experimental studies on blood pressure in shock have, I believe, in some respects obscured the issue. Low blood pressure is surely one of the symptoms of shock, but it is not the only symptom. Again, it is not necessary in the definition of shock to assume the presence of blood pressure so low that the animals can not recover, as there is sufficient clinical evidence that recovery from shock may occur. Furthermore, there may be fatal shock without a very low blood pressure, and there may be very low blood pressure without the condition of shock.

While I do not wish to enter here into a detailed discussion of diagnosis, it seems to me quite safe to state that for the diagnosis of traumatic as well as surgical shock it is necessary to take into consideration the general mental state, the states of the sensibility and motility and the conditions of the cardiac, vascular and respiratory functions.

Returning again to our own experiments, we have seen that in animals of all degrees of vitality, laparotomy and handling of the intes-

tines leads to some degree of general apathy, insensibility and motor relaxation; in other words, to some of the symptoms of shock. This partial shock is not necessarily fatal and concerns functions which are not of immediate vital importance. With the prolongation of the exposure and handling of the viscera, the danger of the involvement of the cardiac, vascular and respiratory functions increases, and the danger is the greater the lower the vital resistance of the animal. The last-named functions are of greater importance for the continuation of life and are, therefore, in the vigorous animal provided with greater factors of safety, so that minor assaults do not easily shake their foundation.

Generalizing our experience, we may say that the sudden opening of any body cavity will frequently cause a partial shock which may consist of the anesthetic condition of the contents of this cavity, a reduction of general sensibility and a general muscular relaxation. When the handling of the contents of the cavity is continued and the powers of resistance of the subject are at a low point, a more or less complete shock develops, in which other more vital functions become involved in varying degree; sometimes the heart, sometimes the vascular system, and sometimes the respiratory mechanism, are predominantly affected. Similar conditions may be brought on by extensive dissections or burning of some parts of the body; it should be borne in mind that one part may perhaps react more readily than another. Beside these intentionally produced or accidental injuries, violent mechanical agitation of some especially sensitive part without actual destruction of tissue might also be capable of calling forth more or less complete forms of shock. All these various methods of producing partial or complete shock represent in one form or another strong stimulations abruptly applied to the normally tranquil nervous system.

What is the nature of that condition which we term shock? We are in the habit of expecting a stimulus to produce or increase an activity. In shock the activity of the functions is depressed or suspended. By what method do the stimulating injuries cause this depression or suspension of activity? The current view is that the depression is a state of exhaustion or fatigue of the functions or of the nerve cells controlling them. In estimating the value of this hypothesis, one should remember that it was first advanced to account for the inhibitory effect of the vagus upon the heart. The objectors to the new idea of inhibition tried to explain the fact of the arrest of the heart's action by assuming that the vagus was the motor nerve of the heart, and that the cutting of the nerve caused fatigue of the heart by overstimulation.

Since this time this has been the favorite hypothesis of some writers to explain any reduction of activity of the nervous system. The fact that no hyperactivity of the function precedes its depression does not seem to have any weight with these writers.

In our own experiments upon the motility of the gastrointestinal canal we have seen that the dissection of the skin produced a suspension of the normal movements which could not depend on fatigue and exhaustion, since the destruction of the cord restored the function of the gut to even greater activity. It was evident that in this case the dissection of the skin gave rise to an inhibition of the motor function of the gastrointestinal canal similar in character to that of the cardiac inhibition. Furthermore, in the studies of the effects of the stimulation of the vagus on respiration, it was found that opening of the abdomen favored the inhibitory response to stimulation to the central end of that nerve. These facts demonstrate that dissections of the skin or opening of the abdominal cavity do not produce exhaustion, but result in a more active inhibition.

On the other hand, Howell has called attention to the fact that the vascular depression in shock is not preceded by increased activity sufficient to justify the assumption of exhaustion from over-stimulation of the center. Furthermore, in the stroke experiments of Goltz, the general paralysis and the anesthesia prevalent during the stroking of the abdomen is never preceded by tetanus or hyperesthesia.

On the basis of these considerations I venture the assumption, which is not new, that the various injuries which are capable of bringing on shock, do so by favoring the development of the inhibitory side of all the functions of the body. This predominance of inhibition makes its appearance at first in those functions which are of less immediate importance to life, and are, therefore, less insured by safeguards protecting their equilibrium. With increased injury the inhibition spreads also to the more vital and, therefore, better protected functions of the nervous system. The early inhibition in the development of shock, of the functions of lesser importance, might even be looked on as being, in a degree, conservative measures of protection of other more important functions of animal life. The restfulness of the body, the painlessness and mental indifference are certainly most desirable conditions in the management of shock of the more vital functions.

We shall say here a few words as to the meaning and importance of inhibition in connection with our problem. The body's functions are clearly constructed on the dual principle. The heart has the accelerators as motor, and the vagi as inhibitory nerves. The vascular system has

in the centrifugal direction vasoconstrictors and vasodilators, the latter having simply inhibitory functions. In the centripetal direction there are nerve fibers which increase the tonus of the vasomotor center, as the fibers within the sciatic nerve, and there are nerve fibers which inhibit and depress the tonus, as the depressor nerve. For the respiratory centers there are fibers which augment inspiration, as certain fibers in the vagus, and others, as the superior laryngeal nerve, which inhibit inspiration. The same holds good for expiration. For the gastrointestinal canal the vagus is essentially a motor nerve and the splanchnic nerve essentially an inhibitor. These instances will suffice to support the contention that the functions are not kept up simply by acting when there is a stimulus to them and by resting when a stimulus is lacking. They are, on the contrary, constructed on the dual principle, on a well-balanced antagonism between excitation and inhibition. During life there is never an absence of stimuli; they stream continually in legions from outside and are ever present in the blood and lymph. The normal state of a function results from a proper balance of antagonistic stimulations, and the important functions are well provided with factors of safety to keep up the normal equilibrium.

Under unusual abnormal conditions, however, there may arise a tendency toward a deviation in one or the other direction; that is, in the direction of excitation or in that of inhibition. With regard to shock, our theory assumes that the injuries which produce shock disturb the equilibrium, causing a tendency toward inhibition. It certainly does not mean reducing the function to a single principle, to inhibition alone; it only means shifting the tendency toward inhibition. Stimulation of nerve fibers which usually cause excitation will still cite, and fibers which cause inhibition will still inhibit and probably inhibit even better than in a normal state. Porter's experiments showing that in shock the depressor is very active, more so even, than when the blood pressure is normal, is far from being evidence against the theory that in shock the vasomotor center is more favorable toward inhibition; on the contrary, it would tend to support this idea.

The assumption that the insufficient activity of several functions during shock is due to a preponderating inhibitory influence refers only to the primary effect. It seems to me self-evident that during the course of shock other influences must become secondarily active. The insufficient activity of one function becomes detrimental to the other, and anemia, asphyxia or even fatigue or other conditions might become operative during the progress of shock.

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CHLOROFORM NECROSIS OF THE LIVER.*

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The occurrence of serious, frequently fatal, poisoning as a sequel of chloroform anesthesia, manifesting itself first several hours or even a few days after the use of the drug, has been brought into prominence through the articles of Ballin, Bevan and Favill, Brewer, Brackett and others in this country, and of Guthrie in England; therefore, it is unnecessary for me to discuss the literature at length, as this will be found fully abstracted to 1905 in the article of Bevan and Favill,[1] and subsequent articles are indexed in the foot notes to this article.

REPORT OF THE CASE.

I desire merely to report a study of both the pathologic anatomy and the chemistry of a typical case, which I had the opportunity of examining at autopsy, through the courtesy of Dr. F. S. Tufts, and to consider certain features illustrated by this case and those so far recorded in the literature. Dr. Tufts has kindly furnished me the clinical history, which follows:

Clinical History.—"The patient, a vigorous young man, was born in Wisconsin in 1878. The family history is negative. He came to Chicago in 1899, and has been employed as a foreman in the hog-casing department of a packing house. In 1900 he married a first cousin, who gave birth to a healthy boy in 1904. His childhood history was negative, and up to 1902 he was strong, robust, and of very good color. In 1902 he lost weight and color, and began to complain of an occasional stomach trouble. He had no acute attacks or colic, but occasionally there was acute distress from gas after meals, with a sensation of fullness. The first acute attack of colic and cramps occurred on Jan. 1, 1907, and was brought on by a hearty packing-house restaurant dinner. I saw him two hours after the attack and found slight tenderness in the umbilical region, but nothing around or near the gall bladder; he returned to work the next day and was free from trouble until March 17. This second attack was apparently caused by fruit salad which he had eaten the day before. At this time I found no fever, some rigidity in the right rectus, but not much tenderness; he had had colic and cramps all night but not severe enough to call me. On the next day, March 18, he went to work, although still a little lame, and the following day visited me at my office, when the gall bladder was found markedly distended; it extended 10 cm. below the costal arch, was freely movable and slightly tender. At this time there was no fever, no icterus, nor even bile in the urine (Gmelin's test). On the next day his condition was about the same, although the temperature was 99.2, pulse 78. The following day (March 21) the temperature was normal and the tenderness was

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1. Bevan and Favill, Jour. Am. Med. Ass'n., 1905, xiv, 691-696.

subsiding, but he was quite pale and complained of feeling very weak; in the evening he was taken to the Englewood Hospital." Here his pulse, temperature and respiration were recorded as normal, and he was prepared for operation, which was performed at 4 p. m. on March 22.

Anesthesia.—The anesthetic was chloroform and it was "given with a free hand" by the anesthetizer, and cyanosis was very marked. The duration of anesthesia, however, was not long, as it is recorded that the patient left the ward for the operating room at 4 p. m., returned at 5 p. m., and was again conscious at 5:30 p. m.

Operation.—When the abdomen was opened the upper surface of the liver was found freshly adherent to the parietal peritoneum, while the lower surface, gall bladder and intestines were bathed with lymph and fresh adhesions everywhere. The gall bladder was thickened, but neither it nor the ducts were distended, and no stones could be palpated. On account of the evidently acute nature of the infection it was deemed wiser not to open the gall bladder, and the bad way in which the patient was taking the anesthetic impelled haste, so the abdomen was closed again without draining the gall bladder.

Postoperative History.—Following the operation the patient slept fairly well and the next day at noon the temperature rose to 99.7, but subsided on the following morning, March 24, although at this time there was a leucocytosis of 17,000. All this day the patient was in good condition, sleeping much of the time, until 11 p. m., fifty-five hours after the operation, when he began to be restless. By 3 a. m., March 25, he began to be delirious, acutely maniacal, and was unconscious from that time on, although he could be roused somewhat by calling. On the morning of this day the temperature at 10:30 was 99.3, pulse 82, respiration 22. The patient was very thirsty, icterus began to appear, and the urine, which before the operation had been normal, now showed much bile, albumin and hyalin and granular casts, but no crystals of leucin or tyrosin could be found. Under the influence of chloral and bromids the patient became more quiet at about 4 p. m., laughter and crying taking the place of the wild delirium previously exhibited. The jaundice had increased during the day. By 3 p. m. the temperature had risen to 103; at 5 p. m. it was 104; at 7 p. m., 106; and at 8 p. m., 107. Death occurred at 9:30 p. m., 100 hours after the operation.

Autopsy.—This was performed at 9 o'clock the next morning, in the undertaker's room, to which the body had been removed. An attempt at embalming with an arsenical solution had been made just before our arrival, but fortunately this was so ineffectually done that practically none of the fluid penetrated the viscera and they were almost unaffected; however, there had been some fluid introduced directly into the peritoneal cavity, which interfered with cultures being made from the peritoneal exudate and gall bladder; while of course blood cultures were made valueless by the intravascular injection.

Autopsy Report.—This is summarized below.

Anatomic Diagnosis: Acute hepatic degeneration and atrophy. Cholelithiasis with chronic suppurative and proliferative cholecystitis. Acute fibrinous pericholecystitis. Suppurative cholangitis with fibrous pericholangitis. Partial occlusion of cystic duct near juncture with hepatic duct. Recent operative incision in right hypochondrium. General icterus. Multiple ecchymoses in serosa of thoracic and abdominal cavities. Hypostatic pulmonary congestion. Right inguinal hernia.

External Appearance: Young man, slenderly built; fairly nourished; very icteric all over the body, especially the face; sclera bright yellow. Scar of old trauma over right tibia. Recent operative incision three inches long in right hypochondrium; also embalmer's incision in right arm. Discolored skin areas from saline transfusion over both pectorals. Right inguinal canal open a short ditsance.

Abdominal Cavity: Distended by clear embalming fluid (arsenic and bichlorid of mercury). (Clinically it was flaccid up to death.) Omentum free. Numerous small blood extravasations throughout omentum. Many hemorrhagic foci, size of pea and smaller, scattered throughout mesentery and retroperitoneal tissue. Several larger suggillations more sparsely distributed. Appendix free; three inches long, no mesoappendix; no changes.

Gall Bladder: Adherent to colon and pylorus by fresh, easily torn, fibrinous adhesions. Surface of gall bladder covered by fibrin, beneath which are numerous hemorrhagic extravasations into the subperitoneal tissues. Gall bladder wall greatly thickened, about 5 to 8 mm. thick. On palpation the bladder apparently semi-solid; cystic duct thickened and distended. Lesser peritoneal cavity free. Diaphragm at fourth rib on both sides. Slight adhesions about spleen.

Chest: The entire mediastinal tissue riddled by ecchymoses, averaging about the size of a pinhead. Pericardium studded with the same. Pericardial cavity normal. Both pleural sacs free from adhesions. Pleura everywhere studded with small ecchymoses.

Heart and Great Vessels: Normal. Portal system free from thrombi.

Lungs: Posterior parts of each lung congested and darker than the anterior and contain much fluid. (Probably part is embalmer's fluid; no clinical indication of edema before death.)

Liver: This is small; weight 1,050 g. The margin is two fingers' breadth above costal margin. The right lobe has been superficially hardened by embalming fluid. The left lobe is not hardened to any extent. The latter is very flabby, pinkish gray in color and looks almost as if decomposed. The anterior margin is very sharp. Surface discolored to a dirty pinkish-gray color and somewhat wrinkled. The right lobe shows the lobular marks with unusual distinctness on the external surface, as a fine network of lighter gray lines with reddish hexagonal areas between. The cut surface of the right lobe shows the same mottling as seen externally, and is of a light yellow tinge. The left lobe is very distinctly yellow; the lobular markings are difficult to distinguish. The consistence is very flabby so that the liver can be folded upon itself. The bile ducts and large vessels show no evident changes. On pressure on ductus choledochus, a purulent yellow fluid exudes into the duodenum from the ampulla of Vater. On incision of gall bladder a yellow muco-pus escapes. In the bladder are over 100 stones, black, hard, varying in size from 3 mm. in diameter down to that of the finest sand. The gall bladder wall is 6 mm. thick. There is nearly total obstruction of cystic duct near its junction with the hepatic duct by a fibrous occlusion (scar tissue) and pressure of a mass of recent fibrous tissue about the duct. The hepatic duct seems to be normal. A few stones occur in the ductus choledochus. The latter shows an inflammation and swelling of the mucosa.

Spleen: Apparently normal. Very much hardened by embalming fluid.

Pancreas: No evidence of fat necrosis, and no other change observed.

Kidneys: Somewhat hardened by embalming fluid. Normal size. Capsule strips normally; no evident pathologic alterations.

Adrenals: Normal.

Histologic Findings.—Liver: There is not a normal liver cell to be found, and very few, indeed, that are not totally necrotic. At first glance the liver resembles an organ that has undergone extensive postmortem decomposition, but it is soon seen that only the parenchyma cells have been affected, and that there are quantitative differences between the conditions in the center and periphery of the lobules. The lobules are somewhat reduced in size and only at the very periphery of the lobules can there be found parenchyma cells that show any approach

to the normal structure; these cells are never more than one or two layers deep from the periportal tissue, and the best of them show cloudy swelling and fine granules of fat. Immediately next to these cells is a narrow zone, representing a width equal to two to ten liver cells, in which the cells consist of a mere meshwork of fat droplets with no cytoplasm remaining and only exceptionally a nucleus. In all the rest of the lobule, which part constitutes from two-thirds to four-fifths of the entire radius of each lobule, is total necrosis of the liver cells; nothing remains of them but the dead bodies of the cells, deeply stained by eosin and evidently greatly reduced both in size and number. There is no thrombosis in the hepatic capillaries, no acute or chronic inflammation, and no evidence of alteration in the bile ducts. By sudan III the necrotic central cells are found rarely to contain small fat droplets, although between them can be found Kupfer cells that are quite fatty. The vacuolated zone near the periphery is composed of cells containing large amounts of fat, and the most normal peripheral cells show numerous fat droplets.

Kidney: Epithelium of convoluted tubules is granular and many of the tubules are swollen shut, and some contain occasional fat droplets; these are especially numerous in the straight collecting tubules. Some of the epithelial cells seem to be necrotic. The glomeruli contain a considerable amount of granular debris, but otherwise no changes. There is no hemorrhage, acute inflammation or connective tissue increase.

Spleen, Myocardium and Pancreas: No changes found, except a small amount of fat in some of the muscle cells of the heart.

Gall Bladder: Diffuse infiltration of the wall with lymphoid cells, plasma cells and some polymorphonuclear leucocytes.

Chemical Examination of Liver.—Immediately after the autopsy the liver was cut into thin slices, and 850 grams of the fresh tissue were placed in a large volume of 95 per cent. alcohol until thoroughly hardened, and then subjected to chemical analysis, the details of which will be published elsewhere.[2] The chief results of this study may be summarized as follows: Among the water-soluble substances obtained by extraction of the liver tissue were considerable quantities of free aminoacids, presumably derived from the proteins of the liver cells through autodigestion; of these aminoacids there were obtained in pure enough condition for identification 0.34 gram of histidin, 0.26 gram of tyrosin; 1.50 grams of leucin, 1.57 grams of glycocoll and 0.58 grams of glutamic acid. The presence of arginin, lysin, and pyrrolidin-carbonic acid could not be definitely established, although there was obtained evidence which indicated that these substances were in the extracts. A further indication of the autolytic destruction of the liver proteins that was going on in this case was the finding of considerable quantities of proteoses, peptones, and probably of polypeptids. Free xanthin and hypoxanthin were also found in the extracts, undoubtedly derived through autolytic disintegration of the nucleoproteins of the liver cells. There was no increase in the gelatigenous substance of the liver, such as has been observed in acute yellow atrophy, since this is the result of regenerative proliferation of connective tissue, which had not begun to take place in the chloroform necrosis liver. The composition of the insoluble coagulated proteins left after thorough extraction of the liver with alcohol, ether, and cold and hot water, was found to be quite the same in this liver as in two normal livers, at least so far as the form in which the nitrogen is bound; whereas a liver from a typical case of advanced acute yellow atrophy showed some loss of diamino-nitrogen. This is shown in the following table giving the results of analyses of these four cases by Hausmann's method:

2. Wells, H. G.: Jour. Biol. Chem., 1908, vol. v.

COMPARISON BETWEEN ACUTE ATROPHY, NORMAL AND CHLOROFORM NECROSIS LIVERS.

	Acute Atrophy.	Normal (anemic)	Normal (congested)	Chloroform Necrosis.
Amid nitrogen	5.5	3.7	4.8	3.9
Humus nitrogen	3.6	3.4	4.9	5.7
Diamino nitrogen	26.2	32.8	30.0	30.0
Monamino nitrogen	64.8	60.3	60.2	60.3

This same insoluble residue, which consisted chiefly of proteins, contained the same amount of sulphur as normal liver extracted under the same conditions. The amount of iron was slightly increased, presumably because the hemolysis that always occurs in jaundice sets free iron-containing pigment which the liver stores up. Phosphorus was found increased by three or four times the amount found in normal livers, and this in spite of the great destruction of nuclei that had taken place. No satisfactory explanation for this increased amount of phosphorus has been found.

There was found 72.4 per cent. of water in this liver, 8 per cent. of fats and lipoids and 18.8 per cent. of dry, fat-free solids, which is somewhat different from the proportions found in typical acute yellow atrophy, as shown by the following table:

	Water.	Fat.	Fat-free Dried Substane.
Normal liver (Quincke)	76.1	3.0	20.9
Normal liver (Wells)	77.6	5.0	17.4
Acute atrophy (Perls)	81.6	8.7	9.7
Acute atrophy (Perls)	76.9	7.6	15.5
Acute atrophy (v. Starck)	80.5	4.2	15.5
Acute atrophy (Taylor)	85.8	2.0	12.2
Acute atrophy (Wakeman)	79.3	...	...
Acute atrophy (Wells)	83.8	2.5	13.7
Acute atrophy (Voegtlin)	78.0	6.6	15.4
Phosphorus poisoning (v. Starck)	60.0	29.8	10.0
Fatty degeneration (v. Starck)	64.0	25.0	11.0
Chloroform necrosis (Wells)	72.4	8.8	18.8

In respect to the amount of water, this chloroform necrosis liver stands between the typical acute yellow atrophy liver and the ordinary fatty liver, just as it does in its histology; that is, there has been some replacement of water by fat, as in the fatty livers, but not so much replacement of protein by water as in typical acute yellow atrophy. These figures emphasize the fact that in chloroform necrosis the amount of fat is distinctly increased, although not so much is found on analysis as might be expected from the microscopic findings. Taylor states that, in the chloroform necrosis liver which he examined, there were 200 grams of fat, which would be about twice the proportion that was found in my case; unfortunately he has not published sufficient details of the analysis to furnish the accurate information desired.

The amount of lecithin and cholesterin in this case was found to be not greatly different from that present in normal livers, and thus again in marked contrast to the liver in acute yellow atrophy, as seen by the accompanying table.

While the total amount of lecithin has decreased, this is only in proportion to the decrease in the total size and weight of the liver; this proportional decrease has gone on in spite of a relative increase in the amount of simple fat, showing the same lack of correlation between the lecithin and the neutral fat which has been observed by others who have determined the lecithin content of organs showing fatty degeneration. Evidently, therefore, the increase in the fat content of the liver in chloroform necrosis is due entirely to neutral fats. The cholesterin, on

the other hand, has apparently remained in about the normal amount, and has not decreased with the lecithin and proteins; this is quite what might be expected from what we know of the tendency of cholesterin, when liberated by degenerating cells, to remain at the place where it is formed.

	Lecithin.				Cholesterin.			
	Normal. (Anæmic)	Normal. (Congestion)	Chloroform Necrosis.	Ac. Atr.	Normal. (Anæmic)	Normal. (Congestion)	Chloroform Necrosis.	Ac. Atr.
Fresh weight, per cent.....	1.6	1.4	1.5	0.45	0.26	0.37	0.52	0.3
Total dry weight, per cent.....	6.3	6.25	6.2	2.9	1.0	1.7	1.9	1.8
Dry, fat-free material, per cent.	7.7	8.0	8.1	3.2	1.25	2.1	2.9	2.1
Ether-soluble substances, per cent	35.3	28.0	17.3	17.6	5.7	7.4	5.9	11.1
Grams in entire liver.....	23.7	22.4	16.0	4.4	3.8	5.95	5.4	3.38

GENERAL CONSIDERATIONS.

If we examine carefully the cases of "delayed chloroform poisoning," as reported in the literature under various titles, it becomes apparent that there are included two fairly distinct types of cases resulting from the same cause, and that these types differ both clinically and anatomically. In one set the patient is usually a child; the clinical manifestations are vomiting, restlessness or extreme excitement, terminating in coma, frequently more or less cyanosis, and sometimes definite air hunger, a sweetish odor of the breath and acetone bodies present in the urine in most of the cases in which they were sought for; in other words, the symptoms resemble in many respects "acidemia" or "acetonemia," under which titles many of these cases have been described. The liver in these cases generally shows more or less fatty change; usually when described carefully the fat is said to have been chiefly in the periphery of the lobules, and there is no mention of necrosis of the hepatic cells in the published accounts of these cases. Generally, fatty degeneration and more or less acute parenchymatous degeneration, sometimes even severe necrosis, are found to have taken place in the kidney. In practically none of these cases has jaundice been observed, and the liver changes have not usually been very severe. To this group belong all but perhaps one or two of the cases described by Guthrie, and the cases of Brackett, Brewer, and Telford and Falconer.

Quite different from this group are the cases of Stocker, Bandler, Erlach, Marthen, Mintz, Ballin, Campbell-Horsfall, Guleke, Cushing, Taylor, Holmes and the one described in this report. Here the clinical picture at first is rather similar to the first group, in that the onset is usually with restlessness, excitation, and delirium, which passes into coma. However, in place of those symptoms which are usually considered as manifestations of acetonemia, there appears a rapidly developing

jaundice, which toward the end is generally very severe. Associated with this jaundice are frequently observed cutaneous hemorrhages. The manifestations resemble in every respect a severe cholemia, associated in some cases with the finding of leucin and tyrosin crystals in the urine. Consequently several of these cases have been reported under the title of "acute yellow atrophy of the liver," which diagnosis is supported in the main by the anatomic findings at autopsy. The liver is usually decreased greatly in size, with wrinkled capsule, friable consistence, and yellowish or red and yellow discoloration; often the organ is so severely disorganized, as in the cases of Taylor and the one here reported, that it may be best described as "putty-like." While there is always more or less fatty increase, this is usually more apparent than real, much of the yellow color commonly described as "fatty degeneration" being due to bile pigments; necrosis is the predominant change, beginning in the center of the lobules, as in typical "idiopathic" acute yellow atrophy.

I have had the opportunity to study the histologic appearance of three typical cases of this kind, including one that was reported by Dr. Bayard Holmes[3] and, through the kindness of Dr. Hektoen, the case reported by Drs. Bevan and Favill, and the resemblance of the findings in all three is very striking. As compared with the histologic picture described above in connection with the case which is the subject of this report, the differences are but slight. The Holmes case differs only in having a slightly wider zone of well-preserved cells in the periphery and in the presence of more leucocytes, especially at the junction of the fatty and the necrotic zones. In the case of Bevan and Favill, which clinically was without jaundice or other evidence of hepatic involvement, the fatty zone is very much wider, and the necrotic central cells contain more numerous and larger fat droplets; the size of each lobule is, if anything, increased rather than shrunken. But, taken all together, the histologic picture is strikingly similar in all three livers, practically identical in fact, and indicates the specificity of the effects of chloroform on the liver.

This necrosis is associated with rapid autolysis of the dead cells, so that in my case the weight of the liver had fallen in four days to 1,050 grams, presumably from a normal weight of from 1,600 to 1,800 grams. As a result of this autolysis, leucin and tyrosin may appear in the urine, and free amino-acids may be found in extracts from the liver itself. Of particular interest is the fact that in all the reported cases of this type, as far as I can find, the patients were adults, varying from 20 to 42 years of age; whereas, in the acetonemia type, the patients were nearly all young children. The Bevan and Favill case, in "a girl, aged 12½ years,

3. Holmes, Bayard: Appendicitis, 1904, p. 214.

with the stature of a woman," seems to lie at the border line between the two groups, for clinically there was no jaundice and the manifestations were of the "acetonemia" type, but histologically the liver, which was enlarged rather than shrunken, showed a considerable amount of central necrosis, although the fatty changes were more marked than in either of the other two cases that I have studied, and the necrosis and autolysis a little less extensive.

Both sexes are represented in each type, with perhaps a slight preponderance of females. Why there should be this difference in the results of delayed chloroform poisoning in children and in adults I do not know, but the number of cases reported is too large to make it seem purely a matter of coincidence. Nearly all reported cases of fatal delayed chloroform poisoning seem to have occurred in the young, only two or three patients having reached the forties. Consequently there appears to be some difference in the liver or in the entire organism between youth and later life that determines this susceptibility to chloroform. In young adults the susceptibility of the liver seems to be particularly great, so that severe necrosis of this organ, with symptoms of hepatic insufficiency, dominates the anatomic and clinical picture.

The changes in the liver, in this second type of delayed chloroform poisoning, are not essentially different from the changes in the early stages of acute yellow atrophy, except that there seems to be a more extensive fatty degeneration and infiltration. In true acute yellow atrophy there is no distinct increase in the proportion of fatty matter in the liver, while the total amount of fat is decreased more or less from the normal, along with the general loss of hepatic substance. In chloroform necrosis there is always more or less fatty metamorphosis noticed microscopically, and in the two cases in which the fat was extracted and weighed, Taylor's and my own, the amount of fat was distinctly increased above normal. It is possible that if one were to secure a liver in chloroform necrosis as long after the onset of the hepatic injury as is the case with acute yellow atrophy, where death occurs usually only after weeks rather than days, the changes might be found still more similar, for I have found that it is possible for a fatty liver to lose much of its fat and to have the fat replaced by fluid during the healing stages of the hepatic lesions produced by hydrazine poisoning.[4] However, even with this disparity of time, the results of analysis of a liver in idiopathic acute yellow atrophy of several weeks' duration are, on the whole, very similar to those obtained with this chloroform necrosis liver,[5] and

4. Wells, H. G.: Pathologic Anatomy of Hydrazine Poisoning, Jour. Exper. Med., 1908, x, No. 4.

5. Wells, H. G.: Chemistry of the Liver in Acute Yellow Atrophy, Jour. Exper. Med., 1907, ix, 627.

I can not take issue with those who have diagnosed their cases of delayed chloroform necrosis as acute yellow atrophy. Nevertheless, I believe that it would be well to reserve this term for those cases of hepatic atrophy which occur without evident cause, and which are characterized by a widespread necrosis of the liver cells without fatty metamorphosis, followed by rapid autolysis and removal of the necrotic cells, and early proliferative activity of the interstitial tissues and the bile duct epithelium. As a particular characteristic of this disease should be mentioned the fact that the organs other than the liver seem scarcely to suffer at all or only secondarily to the hepatic insufficiency. Chloroform necrosis, puerperal eclampsia, and certain violent septicemias, produce changes in the liver that are more or less similar to those described above, but never quite the same, especially in the relatively great injury of other organs and the extent of fatty changes in the liver; therefore, I believe that we would do best to refer to these several forms of hepatic necrosis by the names of the condition causing them, considering the typical "idiopathic acute yellow atrophy" as a pathologic entity, which perhaps may be found to have a specific cause.

As to the reason for the severe effects that chloroform sometimes produces on the liver, some time ago I advanced a hypothesis somewhat as follows:[6]

> Chloroform is a protoplasmic poison for cells of all kinds, stopping their synthetic activities but not seriously impairing their autolytic enzymes. This we see if we add chloroform to a culture or emulsion of bacteria, the cells at once die and begin to undergo autolysis. In view of the nature of the changes that occur in the liver in chloroform necrosis it seems probable that a similar effect has been produced by the chloroform upon the liver cells, that is, their synthetic activities are checked, and autolysis goes on unbalanced by constructive processes. Presumably it is the oxidative enzymes that are chiefly affected by chloroform, for, if these were destroyed, the resulting changes would be exactly what we observe taking place in chloroform necrosis; that is, the lipase would act unbalanced by the normal oxidative destruction of fatty acid and glycerin and so fat would accumulate in the cell, while at the same time synthetic changes, which seem to depend upon oxidative processes and the correlated reductions, would be stopped, and autolysis would assume the upper hand. While at the present time we have no means of determining the correctness of this hypothesis, still it can be said that nothing that is not in harmony with this theorization has yet been learned concerning the processes that take place in chloroform necrosis. Chemical analysis has merely corroborated the anatomic evidence of autoloysis and fat increase in the liver cells.

Just why the liver should only occasionally suffer this serious injury from chloroform is still unexplained. Although in my own case it is probable that excessively free administration of chloroform may have been of influence, in many of the recorded cases this explanation has not been available, for often it is stated specifically that only a small amount

6. Wells, H. G.: Delayed Chloroform Poisoning and Allied Conditions, Jour. Am. Med. Ass'n., Feb. 3, 1906, xlvi, 341.

of chloroform has been used. There is abundant evidence that anything that impairs oxidation favors the occurrence of chloroform poisoning, and diseases that are prone to affect the liver, especially those that of themselves frequently cause fatty changes in the liver, are said, by all who have studied delayed chloroform poisoning, to be important predisposing factors. As a possible explanation of this apparent relation of pre-existing fatty changes in the liver to chloroform necrosis of the same organ, I would make the following suggestion:

Chloroform, like other anesthetics, seems to owe its effect on the nervous system to the fact that it is a strong fat solvent, and hence is taken up by the lipoids of the nervous tissues. This fact was first brought out by Overton and Meyer. The amount of chloroform that a tissue will take up, therefore, depends on the amount of fatty material in it which can dissolve the chloroform out of the blood; this is on the same principle as the method used in the laboratory for separating substances of different solubility in water and ether, water and chloroform, or other immiscible liquids, for the substance in solution distributes itself between the two solvents according to its solubility in each. This phenomenon is manifested when anesthetics are administered to obese persons, whose fatty tissue absorbs so much of the anesthetic that it requires a correspondingly larger amount to affect the nervous system. It would seem probable, therefore, that a fatty liver would abstract much more chloroform from the blood than a normal liver, and that this chloroform would thus act more strongly and for a longer time on the protoplasm of the fatty liver cells than it would in a normal liver.

As to the fact that the necrosis observed in these livers is in the center of the lobules, and that the fatty changes are sometimes central and sometimes peripheral, it would be hazardous to offer an explanation. This distribution of the hepatic lesions in the lobule is always a puzzling question, for, although we can construct explanations on the basis of the fact that poisons first reach the lobule at its periphery and that the oxygen supply is poorest at the center, yet we always find that exceptions are so abundant for any rule we may attempt to formulate that our attempted explanations of the observed facts have no value. For example, in phosphorus poisoning in most of the lower animals we find the fatty changes beginning at the periphery of the lobule; yet in monkeys and apes the changes are said to be central; furthermore, another steatogenetic poison, hydrazine, always produces the fatty changes in the center of the lobule in the same animals in which phosphorus attacks the periphery.

The necrosis of the liver in puerperal eclampsia is ordinarily periph-

eral, and is ascribed to capillary thrombosis. Mulzer[7] found that chloroform administered to rabbits rapidly produces fibrinous thrombi in the capillaries, especially of the lungs, but also in the liver and kidneys. These thrombi are probably initiated by the clumping of injured red corpuscles, and their development is favored by the increased coagulability of the blood, which develops during the anesthesia. It is well known that injection of substances that cause agglutination of the red corpuscles produces extensive necrosis of the liver tissue, but the distribution and appearance of the lesions produced by agglutination thrombi are quite dissimilar to the lesions of chloroform necrosis. In my own specimens, from two cases, I was unable to demonstrate capillary thrombi by Weigert's fibrin stain, and in other cases in the literature the report of the pathologic anatomy is far too incomplete to permit one to judge as to the presence or absence of such thrombi. Of course, it might be possible to explain the anatomic and clinical findings on the basis of capillary thrombosis, if this existed to a sufficient extent, but so far there is no evidence of the occurrence of such a process. It has been suggested that chloroform lowers the normal power of the blood to inhibit autolysis, and if this were extensive enough it might account for the sudden autolysis of the liver that appears in chloroform poisoning. Studies of the inhibiting power of the serum of animals during chloroform anesthesia might throw some light on this.

Two therapeutic hints that have recently appeared seem to be well enough supported by the pathologic and clinical observations to be referred to in closing. J. H. Lyons, of Seattle, in discussing the treatment of puerperal eclampsia,[8] objects to the prevalent custom of suppressing the convulsions by the use of chloroform, often for long periods of time. The similarity of the effects of chloroform and puerperal eclampsia on the liver, and the well-established fact that pre-existing injury to the liver predisposes to delayed chloroform necrosis, are certainly weighty reasons for this caution. It is also quite probable that chloral is not altogether a safe sedative in cases of this kind, since it is known to produce changes in the liver similar to those caused by chloroform. Beddard[9] suggests that in the treatment of chloroform necrosis, and more especially for its prevention in cases where it is deemed necessary to use chloroform in spite of possible existing disease of the liver,

7. Mulzer: Die Auftreten intravitaler Gerinnungen und Thrombosen in der Gefässen innerer Organe nach Aether-und Chloroformnarkosen. München med. Wchnschr., 1907, liv, 408.

8. Lyons, J. H.: Northwest Med., December, 1906.

9. Beddard, A. P.: A Suggestion for Treatment in Delayed Chloroform Poisoning, Lancet, March 14, 1908, p. 782.

the administration of glucose may be of value. This suggestion is based on Rosenfeld's view that poisoned hepatic cells can utilize carbohydrates well, but proteins and fats only poorly, and that consequently when the cells have used up their meager store of carbohydrate they are unable to utilize the proteins and fats that are available, and hence undergo starvation and death. Experiments have shown that feeding of dextrose to animals lessens the amount of fatty degeneration which results from phosphorus poisoning, and presumably it should have some similar effect in chloroform poisoning.

SUMMARY.

The cases of delayed chloroform poisoning described in the literature apparently tend to group themselves into two classes. In one, which affects chiefly children, the symptoms are those of "acidemia" or "acetonemia," without jaundice, and in these cases the changes of the liver are not so very marked, consisting, according to the published descriptions, chiefly of fatty degenerations about the periphery of the liver lobules. The other type is observed chiefly in young adults, and clinically is marked by profound jaundice, cholemia, hemorrhages, and the usual symptom-complex of a rapidly fatal acute yellow atrophy of the liver; anatomically the liver appears much as it does in acute yellow atrophy, being reduced in size, flabby, yellow and showing microscopically an extreme degree of necrosis, beginning in the center of the lobule, with more or less peripheral fatty degeneration. Intermediate cases occur that do not fall distinctly into one or the other of the two types. Histologic study of these cases of the second type, to which the name "chloroform necrosis of the liver" may be appropriately applied, shows a striking constancy of structural changes; these consist of total necrosis of all the liver cells, except those at the periphery of the lobule, with autolytic disintegration of the necrotic cells, and fatty degeneration of those cells that are not necrotic. The capillaries and bile vessels do not seem to be affected; there is no thrombosis and no inflammation or proliferative reaction. Chemical analysis corroborates the histologic evidence of fatty changes and autolysis, there being found a slightly increased amount of fat, and the presence of considerable quantities of free amino-acids, purins, proteoses, peptones and polypeptids, derived from the autolysis of the cells.

The condition in the second set of cases resembles very closely that of typical acute yellow atrophy of the liver, except in the greater tendency to fatty changes. Nevertheless, it seems best for the present to reserve the term acute yellow atrophy to that form of liver necrosis and autolysis

which occurs "idiopathically," and which presents certain features different from chloroform necrosis, puerperal eclampsia and phosphorus poisoning, and which is possibly due to some specific cause. The fact that chloroform seems particularly to affect livers in which fatty degeneration has been previously produced by some other disorder, may possibly be due to the known absorption of chloroform by intracellular fats, which in this case would increase the concentration and duration of action of the chloroform in the degenerated liver cells. Chloroform is a violent protoplasmic poison and, if it were to inhibit or destroy the oxidizing enzymes of the liver cells, the results would presumably be quite the same as those characteristic of chloroform necrosis; hence it seems probable that chloroform produces its effects by acting on the oxidizing enzymes, without corresponding inhibition of the autolytic enzymes and the lipase of the cells.

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MORPHOLOGY OF THE BLOOD IN PERTUSSIS.*

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HISTORICAL.

To Frölich[1] of Breslau belongs the credit of having first called attention to the blood in pertussis. During an epidemic of this disease in the summer of 1897, he examined the blood in fifty-five cases, making total leucocyte counts in all the cases and differential counts in fifteen. In one case he made three counts during three consecutive weeks and in another two counts; in all the other cases the patients were examined but once.

Summarizing his results, he says, in conclusion, that in this disease there is a constant leucocytosis and lymphocytosis which in individual cases may show high values. The highest counts were noted when the number and severity of the coughing spells reached their maximum, and with the disappearance of these the leucocytosis disappeared. He considered, however, that the blood examination would be of no great value because the changes can not be shown early enough in the disease. He also said that complications have no material effect on the number of leucocytes. In making these examinations he was careful to take the blood at a time of day so as to exclude the physiologic digestive leucocytosis.

With the patients making up these fifty-five cases, eight other children were brought to the dispensary by their parents to be treated for whooping-cough; these patients did not have the disease and their blood showed an absence of the characteristic changes.

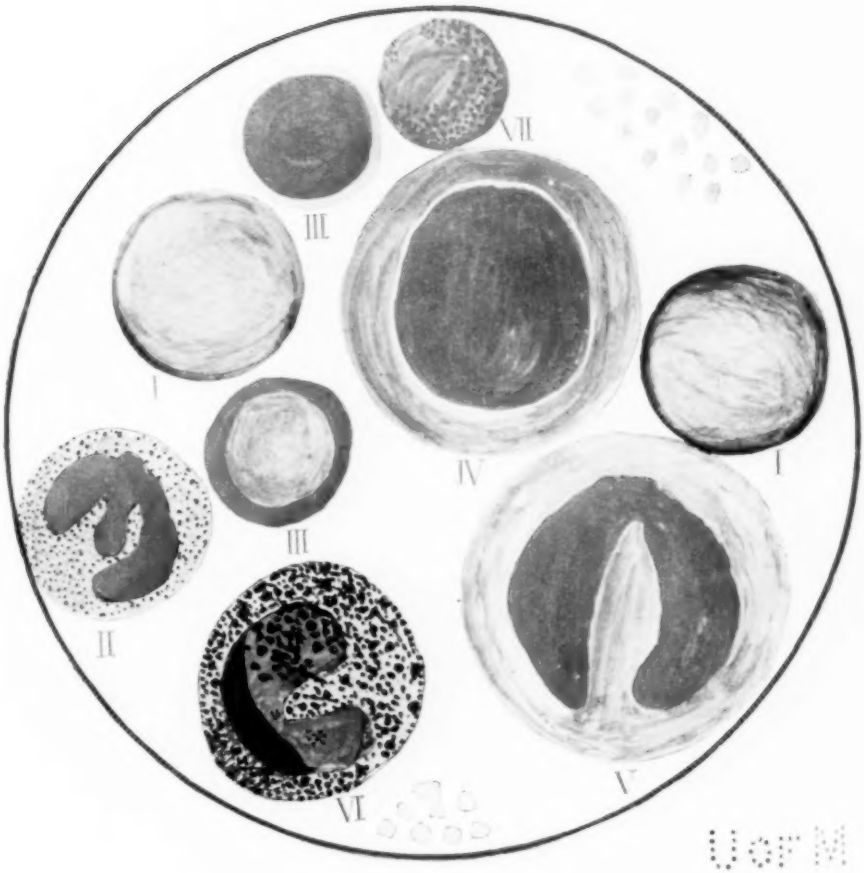
In 1898 Meunier[2] examined the blood in thirty cases of pertussis, making 102 enumerations and ten differential counts. He says that the leucocytosis reaches a higher figure than in any other non-febrile affection of children. The leucocytosis comes early—in some cases occurring in the catarrhal stage, reaching its height thereafter, diminishing irregularly, and its complete disappearance is not realized until after the end of the whooping period. The leucocytosis is more intense among

*Read by invitation before the Academy of Medicine, Nov. 12, 1907.

1. Jahr. f. Kindhlk., 1897, xliv, 59.

2. Compt. rend. Soc. de biol., 1898, l, 103.

NORMAL.



I—Red.
II—Poly.
III—Small } Lymph.
IV—Large }
V—Transitional.
VI—Eosinophile.
VII—Mast Cell.
Blood Plates.

infants of 2 or 3 years, and complications have a moderate influence on the count. The increase of the leucocytes, he says, is due to the increase of the lymphocytes, so that the usual blood formula is reversed. During the time of increasing leucocytosis he figures that the polynuclears are doubled, the lymphocytes quadrupled, transitionals tripled and the eosinophiles not affected.

De Amici and Pacchioni,[3] in 1899, examined the blood in eighteen cases. On studying their tables I find that, while in three cases they made more than three examinations in each case, yet not in one instance did they examine the same child in the three stages of the disease. They eliminated digestive leucocytosis. To eliminate a possible mechanical element in the causation of this leucocytosis they put some of the children under partial ether anesthesia so that there would be no spasmodic coughing at the time that the blood was taken—and from their results were satisfied that the spasmodic coughing itself had nothing to do with the cause of the leucocytosis.

From their studies they conclude that there is in the disease a constant leucocytosis which begins early and continues for a long time after the height of the disease. As a rule, in the first and second stages, there will be found more lymphocytes and in the declining stage a prevalence of polynuclears. They also lay stress on the diagnostic value of the blood examination, because these findings are distinctive and different from those of any of the other respiratory affections with which the disease may be confused.

Stengel and White,[4] in 1901, examined three patients with pertussis and found a leucocytosis and lymphocytosis in each of them. Wanstall,[5] in 1903, reports the findings in fifteen cases of pertussis. He made leucocyte counts in but five of these cases and differential counts in all. In examining nineteen children he found that the fifteen patients with pertussis presented more lymphocytes, while the four that proved not to have pertussis showed more polynuclears.

Cases have been reported by Cabot[6] and Stevens[7] in which very high leucocyte counts have been found. Muggia and Bertolotti,[8] in 1904, treated twenty-five patients with pertussis with inhalations of ozone, from which they claimed highly beneficial results. To prove that this

3. Clin. Med. Ital., 1899, xxxiv, 52.
4. Univ. Penn. Med. Bull., 1902, xiv, 318.
5. Am. Med., 1903, v. 62.
6. "Clinical Examination of the Blood."
7. Lancet, 1902, ii, 791.
8. Riv. de Clin. Ped., February, 1905.

benefit was from the antispasmodic action of the ozone rather than from an antitoxic or antimicrobic action, they set about to examine the blood in a number of these cases. Their findings were: Hyperleucocytosis with predominance of mononuclear cells. These predominating cells they classified as large mononuclears. Their object, however, being the study of the effect from the ozone, they say that "ozone does not change the blood formula, and its action is antispasmodic."

It is interesting to note here that in three severe cases they performed lumbar puncture, and found an increased pressure. When from 15 to 20 c.c. of fluid was removed there was a marked clinical improvement, and the fluid contained an excess of lymphocytes.

In 1905 Grulee and Phemister[9] examined the blood in fifteen cases, making one leucocyte and differential count each in the paroxysmal stage of fourteen and one in case at the end of the catarrhal stage. They conclude that there is a leucocytosis in all stages of the disease, increasing with the increasing frequency of paroxysms and decreasing when the paroxysms become less frequent and severe. According to their method of classification, they found that in the one case examined in the catarrhal stage the lymphocytosis was due to the small lymphocytes and in the other cases the lymphocytosis was due to the large lymphocytes.

In 1906 Churchill[10] reported on the examination of thirty-six cases, making leucocyte and differential counts in all. Out of sixteen cases in the catarrhal stage, fifteen of the patients showed a lymphocytosis. In complicated cases he found a reversion of the blood formula from the prominence of the lymphocytes to that of the polynuclears. From his own work and a complete study of the literature, which at that time consisted entirely of 100 cases, he says, in concluding, that from the catarrhal stage on there is a leucocytosis and lymphocytosis which distinguishes this disease from others with which it may be confounded.

Considering all of this evidence, we may deduce therefrom that in this disease a leucocytosis due to the lymphocytes begins in the catarrhal stage of the disease, attains its height in the paroxysmal stage and then gradually declines with the subsidence of the clinical symptoms. Complications may or may not alter the whooping-cough formula; the predominating opinion is that this formula is of value in the diagnosis of the earlier stages of the disease.

This evidence still left much to be desired to a better understanding of the interesting blood change. Nearly all of the cases reported by the above investigators were those of patients brought to the outdoor clinics.

9. Arch. Pediat., N. Y., 1905, xxii, 595-599.
10. Jour. Am. Med. Assn., 1906, xlvi, 1506.

Over these children they had no control and most of them were examined but once. The findings in the catarrhal stage of the disease had to be compared with the findings in the paroxysmal stage of others and with the declining stage of still other children. The personal equation of each case was lost, and the less prominent changes were entirely overlooked.

THE AUTHOR'S CASES.

During the epidemic of whooping-cough which began in January, 1907, I had the opportunity of studying the blood-picture in this disease and endeavored to carry out the work systematically and more extensively than it had been done before. To do this I traced the probable date at which the patients were first exposed, the time when they first coughed, when they began to whoop and when the coughing ameliorated.

TABLE 1.—CONTROL CASES.

Case No.	Age.	Leucocytes.	Polynuclears.	Lymphocytes Small.	Lymphocytes Large.	Transitionals.	Eosinophiles.
1	1½	10,370	61.0	30.5	4.5	1.0	3.0
2	2	15,280	73.0	23.0	3.5	0.5	0.0
3	2	11,000	82.5	11.5	5.5	0.5	0.0
4	3	12,600	47.5	45.5	5.5	0.0	1.5
5	3	13,300	66.5	26.5	4.5	0.0	2.5
6	3	11,160	53.5	40.5	3.0	0.0	3.0
7	4	10,720	59.5	34.5	4.0	0.5	1.5
8	4	11,300	28.0	55.0	3.0	1.0	13.0
9	4	10,600	37.5	58.0	1.0	0.5	3.0
10	4	7,250	62.0	27.5	5.5	0.0	5.0
11	4	6,800	48.6	45.6	3.6	0.6	1.3
12	4	10,000	54.6	39.1	3.6	0.3	2.6
13	4	17,000	45.1	41.3	1.6	0.3	11.6
14	4	8,600	39.6	52.4	2.8	0.0	5.2
15	4	12,940	32.5	51.3	4.5	1.8	10.0
16	5	11,200	50.0	42.0	5.0	0.0	3.0
17	5	18,300	46.5	45.5	3.5	0.0	4.5
18	5	11,520	51.0	38.0	4.6	0.6	5.6
19	6	9,500	55.0	35.5	3.0	2.5	4.0
20	6	11,000	60.0	29.5	2.5	0.0	8.0
21	6	14,600	60.0	33.5	4.5	0.0	1.5
22	6	7,000	51.25	39.75	7.75	0.25	1.0
23	6	7,200	61.50	32.5	3.0	0.0	3.0
24	6	10,700	63.0	31.5	3.5	0.5	1.5
25	6	9,000	65.6	28.3	1.6	2.0	1.6
26	6	8,120	61.0	31.5	2.5	1.0	4.0
27	7	10,000	69.0	22.5	3.5	0.0	5.0
28	7	9,000	62.5	26.5	7.0	1.0	3.0
29	7	10,400	71.0	23.0	4.0	1.0	1.0
Average.....		10,567	55.74	35.92	4.06	0.54	3.7

The cases are thus classified and in almost each instance a typical cycle can be seen to have occurred. In this way I studied the blood in fifty cases, and my findings are uniform enough to assure the value of the blood examination in diagnosis and to establish the blood-picture for the disease.

The children in which the disease occurred were of the usual whooping-cough age, the greater part of them being institution children previously healthy. Although such children often come from the lower walks of life and have hereditary taints and predispositions, and being institution children live in hygienic surroundings not so good as those enjoyed by children in private homes, yet the results were in no way different from those in cases which occurred in the families of the members of the Academy, whose children represent the highest grade of child life.

These facts assure me beyond doubt that the reaction of the organism to the pertussis infection takes place in a definite way and is associatsd with certain specific manifestations. Of these, the change in the blood formula is one feature.

TABLE 2.—AVERAGE AT DIFFERENT AGES.

Age.						
4	10,578	45.26	44.96	3.7	0.62	6.6
5	10,340	49.0	41.83	4.3	0.2	4.3
6	9,640	59.6	31.28	3.5	0.84	3.0
7	9,800	67.3	24.0	4.8	0.6	1.5

For the sake of brevity I will tabulate in detail only the first thirty cases of this series; not picked cases, but the first thirty that came under my observation. As may be seen (Table 4) the first twenty-nine cases occurred in children from 1½ to 7 years, inclusive, and the thirtieth case occurred in a lady 72 years of age, the mother of a physician. This case I will mention separately. For the normal controls I have made blood counts in healthy children of the same age, living under exactly the same circumstances (Table 1).

As is well known, during the first seven years of life there is a progressive fall in the number of leucocytes, a gradual decrease in the proportion of lymphocytes, and a simultaneous increase of the polynuclears in the circulatory blood. This is distinctly seen in the table of the control cases, excepting in children of the first three years of life. This error, I believe, is entirely due to the small number of cases included. Table 3 gives the average of the control cases at their relative ages.

THE TABULATED RESULTS.

We might compare the individual cases at their relative ages, but, for the sake of brevity, I have arranged each of these tables with sum-totals and averages, and the results are distinct and characteristic. The blood was taken always before meal time, so as to eliminate digestive leucocytosis.

Table 1 shows the counts in the control cases.

Table 2 shows the average counts of the healthy children at their relative ages.

Table 3 shows the counts in those cases of the series in which the first blood examination was made within the first week of the coughing, at the clinical onset of the disease.

TABLE 3.—AT ONSET.

Case No.	Age.	Leucocytes.	Polynuclears.	Lymphocytes Small.	Lymphocytes Large.	Transitionals.	Eosinophiles.
1	1½	30,250	65.3	27.6	4.3	2.0	0.3
10	4	11,760	46.0	47.0	5.0	0.0	2.0
11	4	12,000	69.0	18.5	10.0	1.0	1.5
12	4	17,600	54.5	39.0	4.0	0.0	2.5
13	4	28,000	47.5	41.0	4.5	3.0	4.0
15	4	18,100	49.0	41.0	9.0	1.0	0.0
17	4	9,750	35.0	52.0	6.0	3.0	4.0
20	6	15,660	37.3	52.6	5.1	2.0	3.0
22	6	7,300	47.5	45.5	3.0	0.5	3.5
23	6	33,000	71.0	19.0	4.0	0.5	5.0
24	6	10,500	31.5	53.5	7.5	3.0	4.5
25	6	16,000	40.0	52.0	3.0	3.0	2.0
26	6	12,050	43.0	43.0	5.0	0.0	9.0
29	7	23,800	63.0	31.0	4.0	1.0	1.0
Average.....		17,539	50.06	40.19	5.02	1.42	3.02

TABLE 4.—AT HEIGHT.

Case No.	Age.	Leucocytes.	Polynuclears.	Lymphocytes Small.	Lymphocytes Large.	Transitionals.	Eosinophiles.
1	1½	20,400	49.0	42.0	8.0	0.5	0.5
2	2	40,400	27.5	65.5	4.5	0.5	2.0
3	2	32,250	31.5	65.0	1.5	1.5	0.5
4	2	14,880	33.0	48.5	13.5	1.0	4.0
5	2	88,300	27.5	67.5	3.25	0.25	1.5
6	3	21,200	28.0	60.0	5.0	0.5	6.5
7	3	42,720	24.5	69.0	4.0	0.5	2.0
8	4	36,600	34.5	59.5	4.0	1.0	1.0
9	4	13,300	37.0	52.5	8.0	1.0	1.5
10	4	10,220	47.0	39.0	7.0	1.0	6.0
11	4	25,800	50.0	44.5	3.5	0.0	2.0
12	4	10,800	54.0	38.0	5.5	1.0	1.5
13	4	32,250	37.0	59.5	1.5	0.0	2.0
14	4	14,280	35.5	49.0	12.0	0.5	3.0
15	4	26,240	50.0	46.0	2.5	0.0	1.5
16	4	10,500	35.0	49.0	5.0	0.0	11.0
17	5	15,000	47.5	44.0	4.0	1.5	3.0
18	5	11,850	49.0	41.5	7.0	0.5	2.0
19	6	10,800	40.0	47.0	8.0	1.0	4.0
20	6	41,750	41.6	54.6	3.3	0.3	0.3
21	6	16,200	45.5	39.0	7.5	0.5	7.5
22	6	23,500	38.0	47.0	7.0	2.0	6.0
23	6	13,280	27.0	57.0	9.0	0.0	7.0
24	6	49,280	33.0	62.0	3.0	1.0	1.0
25	6	9,400	44.0	41.0	9.0	2.0	4.0
26	6	9,700	30.0	50.0	13.0	2.0	5.0
27	7	13,300	33.5	53.5	4.0	1.0	8.0
28	7	20,000	29.0	60.0	7.0	1.0	3.0
29	7	34,160	49.0	45.0	3.5	1.0	1.5
30	72	7,000	32.0	50.0	9.0	1.0	8.0
Average.....		22,512	38.06	51.52	6.10	0.78	3.56

Table 4 shows the counts at the height of the disease in the spasmodic stage. The highest counts are seen in those patients who my notes show to have been the sickest children.

Table 5 shows the counts in those cases in which clinically the patients showed a marked improvement. The average time in which the coughing subsided was two months and eleven days.

TABLE 5.—MARKED IMPROVEMENT.

Case No.	Age.	Leucocytes.	Polynuclears.	Lymphocytes Small.	Lymphocytes Large.	Transitionals.	Eosinophiles.
1	1½	5,000	44.0	45.0	6.0	2.0	3.0
2	2	10,500	56.0	27.0	1.0	1.0	15.0
3	2	9,200	45.0	38.0	11.0	3.0	3.0
4	2	12,000	38.0	47.0	4.5	0.5	10.0
5	2	20,200	40.0	52.0	5.5	1.0	1.5
6	3	10,400	44.0	42.5	8.0	1.0	4.5
7	3	6,200	50.0	48.0	1.0	1.0	0.0
8	4	15,500	51.0	34.0	5.5	0.0	9.0
9	4	7,500	42.0	53.0	2.0	1.0	2.0
10	4	6,600	48.0	40.0	4.0	2.0	6.0
11	4	9,400	45.5	44.0	2.0	2.5	6.0
12	4	13,860	60.0	29.5	5.0	2.5	3.0
13	4	11,700	47.0	42.0	6.5	1.0	3.5
14	4	12,200	45.0	47.0	4.0	0.0	4.0
15	4	13,300	48.3	45.0	2.6	0.0	4.0
16	4	7,800	61.0	29.0	6.0	0.0	4.0
17	5	14,200	42.0	42.5	6.0	1.0	8.5
18	5	8,500	50.0	40.0	5.0	1.0	4.0
19	6	10,000	57.5	33.0	2.5	0.5	6.5
20	6	11,750	55.0	35.0	6.0	0.0	3.5
21	6	8,160	49.0	40.0	2.0	4.0	5.0
22	6	11,320	49.0	38.0	3.0	2.0	8.0
23	6	10,200	35.0	49.0	10.0	0.0	6.0
24	6	7,600	37.0	44.0	8.0	2.0	9.0
25	6	8,460	48.0	38.0	6.0	2.0	6.0
26	6	7,800	45.5	42.5	6.5	1.0	4.5
27	7	12,000	48.5	38.0	5.0	1.0	7.5
28	7	9,000	55.0	40.0	2.0	0.0	3.0
29	7	15,428	77.0	18.0	3.0	0.0	2.0
30	72	8,250	57.0	27.5	3.5	3.5	8.5
Average.....		10,451	49.5	39.61	5.1	1.21	5.35

Table 6 shows the counts in the same children after they had been in the country from June to October; at the end of that time they were comparatively in good health.

THE BLOOD-COUNT.

I will now consider the various elements in the blood-count and the course that they pursued. The control will be Table 4.

The Leucocytes as a Whole.—Within a week of the first cough there is a marked leucocytosis, before the change in the differential formula is really noticeable. The leucocytosis steadily increases, reaches its height

in the spasmodic change and then falls by lysis. The average time in which the leucocytes returned to about their normal number was three months and fifteen days after the onset.

The Polynuclears.—Relatively they seem to fall in number, but absolutely they are increased in a moderate degree.

TABLE 6.—EIGHT MONTHS LATER.

Case No.	Age.	Leucocytes.	Polynuclears.	Lymphocytes Small.	Lymphocytes Large.	Transitionals.	Eosinophiles.
1	1½	10,560	54.5	36.5	3.5	0.5	5.0
2	2	10,800	41.0	49.5	3.0	0.5	6.0
3	2	13,800	50.5	41.5	4.5	1.0	2.5
4	2	11,600	50.0	36.5	3.5	0.5	9.5
5	2	.....	...	...	..	..	..
6	3	9,500	57.5	29.0	3.5	3.0	7.0
7	3	.....	...	...	..	..	..
8	4	8,600	57.0	36.0	2.0	1.0	4.0
9	4	6,800	56.0	40.0	3.0	1.0	0.0
10	4	8,800	66.0	25.0	5.0	2.0	2.0
11	4	14,300	57.0	35.0	1.5	0.5	6.0
12	4	12,200	50.0	40.0	2.0	1.0	7.0
13	4	7,800	56.0	35.0	0.0	1.0	8.0
14	4	10,500	69.0	25.0	4.5	1.0	0.0
15	4	20,750	55.5	40.5	2.5	0.0	1.5
16	4	9,060	68.0	24.0	5.0	2.0	1.0
17	5	6,200	47.5	39.5	4.5	0.0	8.5
18	5	10,900	71.0	21.0	5.0	2.0	1.0
19	6	9,300	49.5	37.0	3.0	1.0	9.5
20	6	8,500	47.0	41.0	3.5	0.5	8.0
21	6	9,200	70.0	20.0	5.0	1.0	4.0
22	6	14,300	61.0	21.0	6.0	1.0	11.0
23	6	9,800	63.0	18.0	4.0	4.0	11.0
24	6	11,600	69.0	24.0	2.0	1.0	4.0
25	6	10,600	72.0	19.0	7.0	0.0	2.0
26	6	.....	...	...	..	..	..
27	7	.....	...	...	..	..	..
28	7	1,300	59.0	27.0	5.0	0.0	9.0
29	7	12,100	62.0	32.0	5.0	0.0	1.0
30	72	.....	...	...	..	..	..
Average.....		10,355	58.0	32.0	4.0	1.0	5.0

The Small Lymphocytes.—These are the most prominent elements in the blood change. Their increase begins early in the disease, at times, I believe, before the child coughs. From that time on they continue increasing in number and reach their height in the spasmodic stage. Their fall is gradual, by lysis, and they reach their normal numbers in about three and a half months.

The Large Lymphocytes.—These follow nearly the same course as do the small variety. They increase from the onset, reach their height in the spasmodic stage and decrease thereafter. I did not find that their number was highest in the cases that had the highest grade of small cell

lymphocytosis, nor *vice versa*. In one case a count showed 18 per cent. This was the highest. Nothing else could be associated with it either in the blood-picture or clinically. On carefully studying these cells I find that their numbers are highest at a period which does not exactly coincide with that at which the small lymphocytes are most numerous; it appears to be slightly later. This might mean that these cells represent the final reaction of the lymphocytes or perhaps of the tissues from which these cells are derived, to the pertussis infection. While it is Table 4 that shows their highest numbers, yet that is not the time when they reached their greatest height. These tables show only four of the average number of eight counts that were made in each case.

The Transitionals.—The course of these cells seemed very irregular. They were distinctly less numerous during the height of the lymphocytosis, and comparison with each of the other elements at the different stages of the disease reveals nothing.

The Eosinophiles.—The rôle played by the eosinophiles is distinctive. At the beginning and during the lymphocytosis they are present in about their normal proportions. Somewhere near the third month of the disease, at about the time of recovery, an eosinophilia begins and may continue for several months. In Table 5, which represents the time of marked improvement, out of the thirty cases, twenty of the patients had an eosinophilia averaging 6.75 per cent. Of the remaining ten cases, seven of the patients showed an average count of 8.16 per cent. on the examination immediately before or after the time of the examination in the other cases. This leaves but three cases out of the thirty that at the time of recovery did not present an eosinophile count distinctly above the normal.

On studying the control table (Table 1) we find that the apparently healthy children present a variation of from 1 to 13 per cent. of eosinophiles. Yet the regularity with which the increase of eosinophiles above their normal average proportion occurs in the disease at the time of recovery leads me to believe that the eosinophile has a part of its own in this blood cycle.

These are the more commonly recognized elements of the differential blood count, but in these examinations I have often seen other cells that are worthy of mention.

Mast Cells.—These were conspicuously noted in thirty-eight out of fifty cases and they never exceeded 4 per cent. Their relationship was as follows:

To the total leucocyte count they bore no relation.

To the polynuclears and small mononuclears: Out of thirty-eight cases, at the time when the mast cells were noted, twenty-three showed a greater number of polynuclears; the other fifteen cases showed more small lymphocytes.

To the large lymphocytes: Their presence was noted more frequently about the time the large lymphocytes were high.

To the transitionals: No relation.

To the eosinophiles: No distinct relation, but they occurred more often when the eosinophiles were above the normal.

On the whole, we find that they were more frequent about the time of recovery.

Bilobate Small Lymphocytes.—These cells were very often present, during the stages of active lymphocytosis, which means during the first three or four weeks of the infection.

Degenerated Large Lymphocytes.—The large "basket forms" and smaller forms were also frequently seen during the active lymphocytosis.

Myelocytes with eosin and basophile granules were occasionally noted.

Basophile cells, containing both basophilic and eosinophilic granules, were also noted several times.

Blood plates were seen in very large numbers in two cases after crises from pneumonia complicating the disease. This is the so-called *crise hémotoblastique* of Hayem, who says that the occurrence of large numbers of plates comes with the recovery from the disease (pneumonia). In none of the other cases were they seen in large numbers, although they were always present.

THE ADULT CASE.

The adult case which occurred in a lady 72 years of age was clinically unmistakable. She had the disease at the same time that her three grandchildren were having it. The first count was made during the spasmodic stage and the following ones according to given dates. There was no leucocytosis in this case, but the formula was distinctly reversed. See Table 8.

COMPLICATIONS.

Complications have their effect on the blood formula in a very characteristic way. As will be seen (Table 7) the respiratory organs were most commonly involved and the complications were as follows: Two cases of bronchopneumonia, two cases of pleuropneumonia and one case of suppurative otitis media.

Table 7 shows the effect on the blood formula in each instance. In the pneumonias, the leucocytosis was increased and the polynuclears be-

came at once the prominent cells. As soon as the pneumonias subsided, the leucocytes fell and the lymphocytes became prominent, a reversion to the pertussis formula. De Amici and Pacchioni,[3] Cabot[6] and Churchill[10] report cases complicated by pneumonia, and their findings seem at variance.

TABLE 7.—COMPLICATIONS.

Date.	Leucocytes.	Polynuclears.	Lymphocytes Small.	Lymphocytes Large.	Transitionals.	Eosinophiles.
CASE 1. BRONCHOPNEUMONIA.						
Feb. 9, 1907	49,280	33.0	62.0	3.0	1.0	1.0
Feb. 14, 1907	64,000	49.0	41.5	8.0	0.5	1.0
Feb. 25, 1907	32,000	39.3	54.3	6.0	0.0	0.3
March 10, 1907	13,800	60.0	31.0	5.5	1.0	2.5
CASE 2. BRONCHOPNEUMONIA.						
Feb. 5, 1907	7,300	47.5	45.5	3.0	0.5	3.5
Feb. 20, 1907	18,250	66.0	21.0	5.0	2.6	4.0
Feb. 28, 1907	16,200	45.5	39.0	7.5	0.5	7.5
CASE 3. PLEUROPNEUMONIA. DIED.						
Jan. 26, 1907	39,000	37.0	56.0	4.5	1.0	1.5
Feb. 2, 1907	62,750	53.0	34.5	9.0	1.5	1.5
Feb. 18, 1907	74,000	70.8	22.0	5.5	0.8	0.16
CASE 4. PLEUROPNEUMONIA.						
Jan. 18, 1907	38,800	28.7	65.4	4.53	0.58	0.8
Jan. 24, 1907	53,000	60.3	36.6	2.6	0.3	0.0
Feb. 3, 1907	19,800	30.0	57.5	11.0	1.5	0.0
CASE 5. SUPPURATIVE OTITIS MEDIA.						
Jan. 26, 1907	30,250	65.3	27.6	4.3	2.0	0.3
Jan. 31, 1907	19,830	47.5	41.5	7.5	2.5	1.0
Feb. 26, 1907	10,250	32.0	42.0	18.0	3.0	5.0

TABLE 8.—ADULT CASES.

Date.	Leucocytes.	Polynuclears.	Lymphocytes Small.	Lymphocytes Large.	Transitionals.	Eosinophiles.
March 4, 1907	7,000	32.0	50.0	9.0	1.0	8.0
March 12, 1907	7,700	53.0	38.5	5.0	0.5	3.0
April 18, 1907	8,250	57.0	27.5	3.5	3.5	8.5

A number of the patients in these fifty cases during the paroxysmal stage were sick enough to be put to bed. At these times I examined their chests when I took the blood specimens, and from those observations my belief is that so long as there exists but a severe bronchitis with perhaps small areas of consolidation the lymphocyte formula will be retained, but just as soon as a distinct consolidation is present the formula will be reversed and the polynuclears will predominate.

In the case of suppurative otitis media, the complication was present when the first count was made at the onset of the whooping-cough; after

the ear was drained, the leucocyte count at once fell and the cells assumed the characteristic formula.

In five cases the patients gave a history of having had the disease before. They were patients in Cases 10, 22, 23 and 30. Of these, the patient in Case 10 did not show a lymphocytosis; the others were typical.

SUMMARY.

After a careful study of these cases individually and in the aggregate, in which on an average eight leucocyte and differential counts were made in each case, at regular intervals, the blood cycle in this disease appears to occur as follows:

There is at first a leucocytosis with increase of all the forms; then a small cell lymphocytosis becomes conspicuous and continues to increase when the other forms have reached their limit. The large lymphocytes follow the course of the small ones, but they reach their greatest numbers after the small cells have reached theirs. During the stage of active lymphocytosis, bilobed small lymphocytes are frequently seen as well as numerous degenerated large lymphocytes, especially the basket forms.

Then comes the simultaneous falling of the leucocytosis and lymphocytosis, while the polynuclears begin to resume their normal proportion. A little later the mast cells are observed more frequently, and an occasional myelocyte may be seen. While the leucocytosis and lymphocytosis continue to fall by lysis, an eosinophilia is noted; this continues for a variable time, after which the blood formula resumes its normal proportions. During this entire cycle the transitionals seem unaffected.

If we were to speak of the first and second half of the blood cycle in this disease, we would say that in the first half the lymphocytes are the prominent factors and in the second half the polynuclears and the eosinophiles.

Clinically, leucocytosis is present at about the time the child first coughs; as the coughing goes on, the leucocytosis increases and the lymphocytosis becomes very marked. A glance at the tables gives an idea of the numbers. The height of the leucocytosis is reached in the spasmodic stage, sometimes early, and sometimes in the latter part, the sickest children showing the highest grade of leucocytosis. About the time that a marked improvement is noted in the child the leucocytosis has decreased, the polynuclears have increased and the eosinophilia is present. This eosinophilia continues for a variable time.

Little more need be said of the distinct value of blood examination in the early diagnosis of the disease. Within the last two months I have

been able to make correctly for other physicians three negative and two positive diagnoses before clinical signs were decisive.

I wish to express my thanks to Dr. Ewing W. Day, Dr. T. J. Elterich, Dr. P. J. Eaton and Dr. Lawrence Litchfield for the clinical material that they have placed at my disposal in carrying on this investigation, and to Dr. E. G. Matson and Dr. G. Conti for their kind assistance in translating the original articles from which I have quoted in the first part of this paper.

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EXPERIMENTS WITH AN ASH-FREE DIET.*

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The introduction of standard test diets into clinical medicine has distinctly advanced our knowledge of human metabolism and furnished many useful data for diagnosis, prognosis and treatment. Such are the Ewald test breakfast, the diet of Schmidt and Strassburger for the study of diseases of the gastrointestinal tract and the proteid-fat diet employed in diabetes. Although these various diets were excellent, they threw light on only the more superficial phenomena of metabolism, and it was to be expected that other variations in the diet would be planned which would penetrate into the more fundamental processes of the body. It is to the credit of Taylor[1] that he devised such a diet in 1904 and had the temerity to live on it until unusual symptoms occurred.

Admirable as was the conception and interesting as were the results of Taylor's experiments with an ash-free diet, one of his observations and the interpretation he later placed on it were so at variance with prevailing ideas as to attract our attention. He writes: "On the ninth day a colleague noted in the breath a strong odor of acetone. Investigation thereon revealed in the urine notable quantities of acetone and diacetic acid without β-oxybutyric acid." At the session of the Association of American Physicians held in 1907 this observation was cited by Taylor as an argument against the generally accepted theory of acidosis of the β-oxybutyric type, which ascribes its occurrence to the lack of oxidation of carbohydrates in the metabolism. His criticism apparently was fully justified, because, according to his experiment, an acidosis developed in a healthy individual on a diet which maintained equilibrium and contained 200 grams of carbohydrates which were known to be assimilated.

The overthrow of any theory which has served so many useful purposes as the secondary oxidation theory proposed by Nasse and adopted by Naunyn can hardly be considered accomplished by a single experiment. It, therefore, seemed well worth while to repeat the work, particularly because, so far as we are aware, no further evidence has been offered which would confirm it. The mere detection of acetone in the breath by

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1. Taylor: Studies on an Ash-free Diet, Univ. of Calif. Pub., Pathology, 1904, i, p. 71.

the sense of smell can not be accepted as a sufficient guarantee of its presence. Indeed, Folin's recent observations[2] make it probable that the so-called "acetone breath" has nothing to do with acetone. The actual quantity of acetone in the urine is not given by Taylor, but at the most the acidosis must have been slight, because the ammonia-nitrogen nitrogen ratio reached but 9.5 per cent. Convincing proof that acidosis of the acetone type was due to the withdrawal of salt might have been afforded if an acidosis thus produced had disappeared on the addition of salt to the diet without other change in the plan of the experiment.

Our experiments followed exactly the methods suggested by Dr. Taylor. Two healthy medical students, Mr. Sawyer and Mr. Smith, consented to act as subjects.[3]

The daily diet consisted of the whites of 18 eggs, 120 gm. olive oil, and 200 gm. of crystallized sugar. The albumin was prepared in the following manner: Eighteen hundred c.c. distilled water (100 c.c. to the white of each egg) were heated in a double boiler up to 56 degrees C. The whites of the eggs, previously broken up with a glass rod until homogenous, were then poured in, and at first stirred briskly, but later more slowly until the temperature reached 100 degrees C. Twelve c.c. of acetic acid, diluted by one-fifth, were added and the clear fluid decanted off from the precipitated albumin. The precipitate was thoroughly mixed with 1,000 c.c. distilled water, heated nearly to the boiling point and again decanted, this procedure being repeated three times. The albumin was then transferred to a large Buchner filter and again washed three or four times with hot distilled water. The final filtrate was nearly free from chlorin. The sugar was given in the form of rock candy, of which the ash was non-weighable. The olive oil was washed half a dozen times in a large separating funnel with distilled water. Distilled water alone was drunk and in measured quantities.

Bone-black was used in the demarcation of the stools and was taken with the last regular meal, which was twelve hours before the commencement of the experiment, and again on its completion just before a return to an ordinary diet.

The first experiment was begun Nov. 29, 1907, and continued for thirteen days. Mr. Sawyer's observations during this period are given in his own words. He writes:

2. Folin, Otto: Chemical Problems in Hospital Practice, Jour. Am. Med. Ass'n., 1908, I, p. 1391.

3. Mr. Sawyer and Mr. Smith lived at the New England Deaconess Hospital during the course of the experiment, and to that institution we are much indebted for the many courtesies we received.

The albumin was the most disagreeable part of the diet. I used a syrup with this so as to give it a taste, and in this way it was more easily swallowed, but to the end this proved to be the most irksome part of the experiment. During the time of the dieting I worked between seven and eight hours at the school, at least half of which time I was standing. I spent about two hours of each of the two Sundays that intervened in walking. I slept longer than I usually do, averaging about nine and one-half hours in the day. There were two nights, however, during which I lost about three hours on account of indigestion. With the loss in weight there was also loss in strength, and I found myself more easily winded and more easily tired. On some of the evenings of the more strenuous days I was quite exhausted. On two occasions I had a slight fainting attack. Three evenings before the termination of the experiment I had some symptoms of indigestion, namely, the distress from abdominal distension, hiccough and some belching of gas. My appetite throughout was good, at times ravenous, but not for the ash-free diet, to which I never looked forward. What discomfort there was to the experiment did not progress from first to last. Some of the days earlier in the experiment were more trying than the last.

The diaphoresis which Dr. Taylor observed throughout was noted neither by Mr. Sawyer nor observed by us. Mr. Sawyer's symptoms were not progressive in character, and in this respect he differed both from Dr. Taylor and Mr. Smith. The daily quantity of chlorin in the urine steadily decreased, and on the tenth day reached 0.22 gm., but as the breath and urine gave no evidence of the presence of acetone or diacetic acid the experiment was continued. On the eleventh day the chlorin remained the same, but on the twelfth day it fell to 0.17 gm., or 0.02 gm. less than the lowest limit reached by Taylor. Tests for acetone and diacetic acid still being negative, the diet was continued for another twenty-four hours. The chlorin on this, the thirteenth, day was the same as on the twelfth, but acetone and diacetic acid still failed to appear, and the experiment was, therefore, discontinued. On two subsequent days, namely the second and fourth, the urine was again collected.

The reaction of the urine was acid throughout, and daily tests failed to reveal the presence of albumin, sugar or, as already recorded, acetone or diacetic acid. Le Nobel's test was used for the determination of acetone, and Gerhardt's ferric chlorid test for the diacetic acid. With few exceptions these were performed in the presence of Dr. Folin. The color of the urine was uniformly normal for the first nine days, but became slightly high on the tenth and eleventh and distinctly high on the twelfth and thirteenth. Indican was present in variable quantities as shown qualitatively, gradually decreasing from the first to the sixth day, and then gradually increasing up to the end of the experiment. The urinary sediment gave no evidence of disease of the kidneys. Tables 1, 2, and 3 give the analytical details. The nitrogen was estimated by

the Kjeldahl method, and the ammonia, creatinin, sulphates and total sulphur by the Folin method.[4]

The weight of the dried feces was 121.68 gm., or about 9.0 gm. per day. This is two or three times the weight of the feces of a starving individual. The total quantity of fat in the feces amounted to 53.2 gm., and as the total fat in the diet was 1,560 gm. the total quantity of fat absorbed was 96.6 per cent. The total nitrogen in the feces was 6.05 gm. If the total nitrogen in the diet for the thirteen days is estimated at (11.5 x 13 =) 150 gm., the percentage of nitrogenous food absorbed was 96.

The excellent absorption of the protein and fat is striking and deserves emphasis. It is a most useful point to bear in mind in the treatment of patients. So much has been attributed to the psychic phenomena of digestion that it is well occasionally to have proof that an uninviting and positively distasteful diet, which does not awaken the least suspicion of an appetite, may be thoroughly assimilated.

It is evident from the table that Mr. Sawyer was in nitrogenous equilibrium, because the total nitrogen for the thirteen days was nearly constant, varying from a maximum of 10.7 gr. to a minimum of 12.18 gr., the daily average being 11.5 gm.

The chlorin is the center of interest, because this inorganic salt comprises such a large percentage of the inorganic salts in the urine, and further because of the importance which recent work has assigned to it in metabolism. Its gradual diminution during the thirteen days is mathematical proof of the accuracy of the experiment. The amount of chlorin excreted, 12.94 gm., corresponds to the figures which were obtained in the experiments on Cetti and Breithaupt and those of Belli and Wundt. In the first two days more salt was excreted than in the remaining eleven days, a striking proof of the tenacity with which the body retains its chlorin. For the last five of the thirteen days of the experiment the excretion was practically constant at 0.2 gm. The data show well the limitations of the withdrawal of salt, and again furnish proof that only about 15 per cent. of the total chlorin in the body can be removed. On the conclusion of the experiment Mr. Sawyer returned to his ordinary diet, eating, however, with moderation. Two days later the total quantity of chlorin excreted was only 3.5 gm., despite the fact that he had used rather more salt than was customary, but after four days of the ordinary diet the chlorin amounted to 25.76 gr., and the quantity of urine reached a total of 4,090 c.c. For this great increase

4. Folin: Jour. Biol. Chem., 1906, i, 131.

in the excretion of salt and water we have no explanation, and speculation is unprofitable because of the unknown character of the ingesta. In the next experiment we attempted to follow this point more closely.

The weight can be brought into connection with the chlorin because the two varied together. Sawyer lost 2.8 kg. during the first three days of the experiment, but in the remaining ten days only 2.5 kg. Taylor reports a loss of 1.5 kg. "during the period." Probably this statement refers to the change in weight from his third to ninth day. Quite as striking as the loss of weight during the experiment was the gain of 4.1 kg. in the first seventy-two hours following its completion. Whereas the addition of salt to the diet of a healthy person has little effect due to its ready elimination, the withdrawal of salt from the diet is of more significance, because along with it goes a lowering of body weight by removal of water. This fact must always be borne in mind in any experiment in which weight is a factor.

The loss of 10 per cent. of body water is said to produce a moribund condition in thirsting animals, but the conditions of our experiment were different in that the loss of water was coincident with the loss of salt, and so in a way physiologic.

The intake of water was nearly constant, diminishing slightly as the experiment progressed. The possibility that this diminution in the supply of fluid was concerned in the loss of weight was excluded in the second experiment by keeping the intake of water at a constant level of 2,000 c.c. Less fluid was voided than water drunk, corresponding to the well-known fact that a considerable percentage of the water excreted passes out by the lungs and skin. Thirst was not a symptom in the experiment, and, indeed, would appear to vary with different individuals. Thus Taylor (weight 80 kg.) desired over two liters of water daily, Sawyer (weight 70 kg.) was comfortable with 1,300 c.c., and Smith (weight 55 kg.) found only a little less than two liters sufficient. No constant relation can be drawn between the intake of water and the excretion of urine in this experiment.

A steady diminution in the excretion of phosphoric acid took place, but this was not as marked as was the decrease in chlorin. Our values for phosphoric acid are calculated as P_2O_5, while Taylor's are estimated in terms of PO_4. The actual quantity of phosphorus excreted, therefore, was a trifle lower in Sawyer's case than in Taylor's experiment.

The quantity of ammonia was fairly constant from beginning to end, varying from 0.94 gm. on the first day to 1.26 gm. on the tenth. The ammonia-nitrogen nitrogen ratio was nearly uniform throughout. In percentage as well as in absolute quantity it was, however, slightly higher

than the results recorded by Folin.[5] This is readily accounted for by the fact that in our experiment the alkalin salts of the egg whites have been removed.

The creatinin was the most constant factor of all, the lowest quantity being 1.47 gm. and the greatest 1.6 gm. The percentage of creatinin-nitrogen to the total nitrogen varied from 4.6 to 5.4. This percentage is greater than Folin found to be the case with his normal diets, but less than that of healthy individuals on his cream-starch diet. This variation in percentage is accounted for by the total protein of the ash-free diet being considerably lower than that of the standard diet and greater than that of the cream-starch diet. The total quantity of creatinin, however, was practically the same; thus Folin found the average for thirty normal urines to be 1.55 gm. creatinin, and the average in Sawyer's case was 1.54 gm. This is identical with the calculated value for creatinin for an individual of Sawyer's weight, namely 1.54 gm. (22 mg. creatinin per 70 kg. body weight), a further illustration of its dependence on body protein rather than on the protein of the food.

TABLE 1.—INTAKE OF WATER, URINARY ANALYSIS, WEIGHT.

Day.	H_2O	Urine	Sp.	P_2O_5	Cl.	Weight
	c.c.	c.c.	Gr.	gm.	gm.	kg.
1	1470	1720	1012	1.29	4.60	70.2
2	1550	1810	1010	1.29	2.52	...
3	1560	1430	1012	1.28	1.88	...
4	1290	930	1017	1.20	0.87	67.4
5	1290	1100	1013	1.43	0.69	...
6	1545	1170	1012	1.04	0.48	66.6
7	1200	850	1015	1.15	0.46	...
8	1125	1000	1013	0.78	0.40	66.1
9	1290	1160	1011	0.95	0.26	...
10	1200	860	1015	0.89	0.22	...
11	1260	650	1018	0.76	0.22	...
12	1215	510	1023	0.79	0.17	65.1
13	1170	560	1023	0.86	0.17	64.9
14	....	....	....	...	...	...
15	....	940	1029	...	3.50	...
16	....	....	....	...	...	69.0
17	....	4090	1017	...	25.76	...

The uric acid nitrogen was also practically constant, but the percentage was considerably lower than found by Folin in his normal urines. This is in conformity with his idea that the actual amount of uric acid diminishes along with the diminution of the total nitrogen, even apart from the purin nitrogen of the food.

5. Folin, Otto: Approximately Complete Analyses of Thirty "Normal" Urines, Am. Jour. Physiol., 1905, xiii, 45; Laws Governing the Chemical Composition of Urine, Am. Jour. Physiol., 1905, xiii, 66.

The urea represents the chief variable in nitrogenous metabolism. It was low in this experiment, due undoubtedly to the constancy of the excretion of creatinin and the diminution in total nitrogen. Our values for the undetermined nitrogen correspond to those usually found.

TABLE 2.—NITROGEN METABOLISM IN EXPERIMENT ON SAWYER.

Day.	Total—N.	Urea—N.	Ammonia—N.	Creatinin—N.	Uric Acid—N.	Undetermined—N.	Urea—N.	Ammonia—N.	Creatinin—N.	Uric Acid—N.	Undetermined—N.
	gm.	gm.	gm.	gm.	gm.	gm.	P.C.	P.C.	P.C.	P.C.	P.C.
..	....	*20.7*	0.94	*1.60*	*0.18*	...	...	..	..	..	..
1	11.49	9.66	0.78	0.58	0.06	0.41	84.1	6.8	5.0	0.5	3.6
..	....	*18.*	1.02	*1.47*	*0.16*	...	...	..	..	..	..
2	10.27	8.39	0.85	0.55	0.55	0.43	81.7	8.3	5.4	0.5	4.1
..	....	*20.6*	1.04	*1.58*	*0.20*	...	...	..	..	..	..
3	11.67	9.62	0.87	0.59	0.06	0.53	82.5	7.5	5.0	0.5	4.5
..	....	*18.8*	1.12	*1.51*	*0.22*	...	...	..	..	..	..
4	10.73	8.75	0.93	0.56	0.07	0.42	81.5	8.7	5.2	0.7	3.9
..	....	*18.9*	1.13	*1.56*	*0.22*	...	...	..	..	..	..
5	10.86	8.81	0.94	0.58	0.07	0.46	81.1	8.7	5.4	0.6	4.3
..	....	*19.1*	1.17	*1.53*	*0.21*	...	...	..	..	..	..
6	10.91	8.74	0.97	0.57	0.07	0.56	80.1	8.9	5.3	0.7	5.0
..	....	*19.4*	1.15	*1.54*	*0.19*	...	...	..	..	..	..
7	10.72	8.84	0.96	0.57	0.06	0.29	82.5	9.0	5.3	0.6	2.7
..	....	*22.7*	1.24	*1.50*	*0.21*	...	...	..	..	..	..
8	12.18	10.02	1.03	0.56	0.07	0.50	82.0	8.5	4.6	0.6	4.3
..	....	*21.2*	1.24	*1.59*	*0.22*	...	...	..	..	..	..
9	11.86	9.65	1.03	0.59	0.07	0.52	81.4	8.7	5.0	0.5	4.4
..	....	*20.7*	1.26	*1.51*	*0.20*	...	...	..	..	..	..
10	11.54	9.23	1.05	0.56	0.06	0.64	80.0	9.1	4.8	0.5	5.6
..	....	*17.9*	1.15	*1.55*	*0.19*	...	...	..	..	..	..
11	10.07	8.16	0.96	0.58	0.06	0.31	81.0	9.6	5.8	0.6	3.0
..	....	*18.8*	1.24	*1.51*	*0.16*	...	...	..	..	..	..
12	10.99	8.77	1.03	0.56	0.05	0.58	79.8	9.3	5.0	0.5	5.4
..	....	*20.9*	1.21	*1.51*	*0.16*	...	...	..	..	..	..
13	11.69	9.37	1.01	0.56	0.05	0.70	80.4	8.6	4.8	0.4	5.8

The total sulphur in the urine was only about one-third that excreted by individuals living on the stardard normal diet. This must be borne in mind in the interpretation of the results obtained for inorganic and ethereal sulphates and neutral sulphur. The ethereal sulphates diminished in the same proportion as the total sulphur with the result that the percentage of ethereal sulphates remains the same as that obtained for the healthy man on the stardard normal diet. The actual quantity of neutral sulphur, however, did not decrease but stayed practically unchanged. As a result the percentage of neutral sulphur in the urine rose from the usual average of 5 to an average of 15.3. Neutral sulphur thus behaves in a similar manner to creatinin. Our results approximate those obtained by Folin in his experiments with the low pro-

tein or starch and cream diet. The inorganic sulphates are here the variable which offsets the increased percentage of neutral sulphur.

Our first experiment thus failed to confirm Taylor's observation on the influence of a salt-free diet on the production of acetone. The question thus stood simply one experiment against another, and it seemed wise to perform a third under slightly different conditions to eliminate the personal equation. The subject, Mr. Smith, weighed much less than either Dr. Taylor or Mr. Sawyer, namely, 55 kg. The experiment was begun on February 15 and ended February 26, but for four days previous to it Mr. Smith lived on a diet poor in salt. By means of this preliminary and partially salt-free period several days were saved and we were enabled to study the effect of the addition of salt in the latter part of the experiment without too great prolongation of the same. The plan was successful, for on the first day the chlorin in the urine was found to have fallen to 1.43 gm. The details of the experiment were the same as above reported. Mr. Smith found the diet quite as unpalatable as did Mr. Sawyer. On the second day he records in his notes: "Felt well except for slight nausea after meals." The nausea persisted, but on the fifth day was less and did not return until the ninth day. Flatulency was noted on the third day with cramp-like pains and heaviness in the epigastrium, and on several of the days the stool was loose. Some loss of energy was manifest on this and the subsequent days, but it had disappeared by the seventh, when the record states, "No nausea, felt well," and on the eighth, "No nausea, appetite good." The ninth day of the experiment was a trying twenty-four hours; "considerable nausea all day, had great difficulty in eating my meals on account of the nausea and sense of fulness. Felt weak and in low spirits, some abdominal distress," but the symptoms improved the following morning (tenth day); "passed a good night and felt much better, nausea, however, was marked all through the forenoon." Twelve gm. salt were now added to the daily diet, and the following change in the record is interesting: "At lunch took salt for first time with great relish. All nausea and epigastric distress disappeared after lunch; in evening felt very decided increase in strength and energy." Eleventh day: "No nausea or distress of any kind, great improvement in tone, physical and mental." It is only fair to state that Mr. Smith was aware that within three days from the commencement of his taking salt the experiment would definitely end, whereas up to this point the duration of the experiment was indefinite. He himself felt that "hope long deferred maketh the heart sick," and was not positive that the improvement in his feelings was wholly due to the salt.

The urine was examined for the first ten days daily for albumin, sugar, acetone and diacetic acid, but all of these substances were absent. The color remained normal throughout. The examination of the urinary sediment revealed no abnormal elements. Table 4 contains the result of the analyses.

Considerable difficulty was experienced in drying the feces. They were, therefore, first extracted with petroleum ether, and this extract made up to 1,000 c.c. The fat and nitrogen were then determined in each separately and the results combined. Before extraction the weight of the feces was 113 gm.; after gross extraction, 51.62 gm. dried to constant weight. The total quantity of fat extracted from the feces was 80.30 gm., and, as the amount of fat ingested during the nine days was

TABLE 3.—SULPHUR METABOLISM IN EXPERIMENT ON SAWYER.

Day.	Total Sulphur.	Inorganic Sulphates.	Ethereal Sulphates.	Total Sulphates.	Neutral Sulphur.	Inorganic Sulphates.	Ethereal Sulphates.	Total Sulphates.	Neutral Sulphur.
	gm.	gm.	gm.	gm.	gm.	P.C.	P.C.	P.C.	P.C.
1	0.96	0.71	0.05	0.76	0.20	74.0	5.2	79.2	20.8
2	0.97	0.76	0.06	0.82	0.15	78.3	6.2	84.5	15.5
3	0.99	0.79	0.06	0.85	0.14	79.8	6.1	85.9	14.1
4	0.98	0.82	0.06	0.88	0.10	83.6	6.1	89.7	10.3
5	1.04	0.81	0.08	0.89	0.15	77.9	7.7	85.6	14.4
6	1.09	0.86	0.07	0.93	0.16	78.9	6.4	85.3	14.7
7	1.06	0.83	0.07	0.90	0.16	78.3	6.6	84.9	15.1
8	1.17	0.90	0.10	1.00	0.17	76.9	8.6	85.5	15.5
9	1.15	0.90	0.05	0.95	0.20	78.3	4.3	82.6	17.4
10	1.12	0.88	0.08	0.96	0.16	78.6	7.1	85.7	14.3
11	1.01	0.80	0.05	0.85	0.16	79.2	5.0	84.2	15.8
12	1.08	0.85	0.07	0.92	0.16	78.7	6.5	85.2	14.8
13	1.10	0.86	0.07	0.93	0.17	78.2	6.3	84.5	15.5

1,080 gm., the quantity of fat absorbed was 92 per cent. The nitrogen in the dried feces amounted to 2.992 gm. If the nitrogen in the diet is reckoned as 103.5 gm., the absorption of nitrogen was 97 per cent.

It was intended to allow but 1,500 c.c. of water daily, but thirst became so troublesome that this quantity was increased on the first day and permanently changed to 2,000 c.c. from the fifth day on. It is interesting to note that the quantity of urine was only slightly greater than in the experiment with Sawyer or in Taylor's experiment. The average daily quantity of urine in Taylor's experiment was 1,172 c.c., in Sawyer's 1,240 c.c., and in Smith's 1,445 c.c.

The chlorin was but 1.43 gm. on the first day, due, as has been said, to the partial salt-free diet for the previous four days. It then decreased with slight variations until on the ninth day the total quantity of chlorin

was 0.17 gm., the limit reached in the experiment with Sawyer, and 0.2 gm. lower than that attained by Taylor. No sign of acetone or diacetic acid appearing, 12 gm. of salt (7.11 gm. chlorin) were added to the diet. It will be seen that nearly the whole of this quantity was retained in the body, for on the following day only 1.6 gm. were eliminated, and even on the next day only 2.26 gm. chlorin, but during the third day of the administration of salt the chlorin excreted showed a decided increase, and presumably an equilibrium was soon obtained. Neither on these three nor during the following days was a polyuria, as in Sawyer's case, observed. Thirty-one per cent., or 12.83 gm. chlorin, was retained in these three days.

TABLE 4.—INTAKE OF WATER, WEIGHT, URINARY ANALYSIS IN EXPERIMENT ON SMITH.

Day.	H^2O c.c.	Urine c.c.	Total N^3 gm.	NH^3 gm.	Ammonia—N P.C.	P^2O^5 gm.	Sp. Gr.	Cl. gm.	Weight kg.
1	1820	1810	10.9	.58	4.4	2.08	1009	1.43	*55.5
..	.....	.....	...	...	..	...	....	...	54.8
2	1500	1400	11.1	.61	4.5	1.09	1009	1.11	54.3
3	1500	1190	9.8	.64	5.4	.85	1010	.65	54.1
4	1500	1340	9.7	.80	6.6	.85	1008	.49	53.6
5	2000	1250	8.4	.75	7.3	.81	1008	.46	53.3
6	2000	1730	10.4	.98	8.2	.89	1007	.63	53.1
7	2000	1360	9.8	.94	7.9	.80	1008	.25	53.1
8	2000	1540	9.9	.94	7.9	.74	1007	.28	52.7
9	2000	1400	9.9	.96	7.9	.72	1009	.17	52.4
		ADDITION OF 12 GRAMS NaCL TO DAILY DIET.							
10	2000	670	10.1	1.08	8.8	.42	1018	1.06	53.2
11	2000	510	9.6	1.21	10.3	.50	1026	2.26	54.2
12	2000	980	11.2	1.32	9.7	.88	1018	4.64	54.6

*Weight at commencement of experiment; other weights are those obtained at close of each subsequent twenty-four hours.

The loss of weight was less than in Sawyer's case. The reason is evident, because in the few days preceding the experiment the salt in the diet had been restricted, and during this period the weight fell about 1 kg. On the morning of the tenth day the weight was 52.4 kg. Coincident with the administration of salt this rose in the following seventy-two hours 2.2 kg. Corresponding to this increase in weight was a retention of water by the body which is at once manifest by the diminution in the urine during this period.

The average quantity of nitrogen eliminated in the urine per day in Taylor's experiment was 10.04 gm., in Sawyer's 11.2 gm., and in Smith's experiment 9.99 gm. The closeness of the three results is of considerable interest because of the difference of weight of the three individuals, Dr. Taylor weighing 80 kg., Mr. Sawyer 80 kg., and Mr. Smith 55 kg. The ease of the establishment of nitrogenous equilibrium on the same

diet for these different weights is, of course, well known, but ever striking. The absorption of protein in Smith's case, as in Sawyer's, was excellent. The addition of salt to the diet increased the elimination of nitrogen in the urine, despite its smaller volume, by 3 per cent., but this is a quantity too small to be of significance. This observation corresponds to the more recent views on the action of salt on nitrogenous metabolism.

TABLE 5.—METABOLISM IN EXPERIMENT ON DIABETIC PATIENT.

Day.	Vol.	N.	NH_3	Urine Total Sugar.	Total Carb.	$NaHCO_3$	Carb. Bal.	Cl.
	c.c.	gm.	gm.	gm.	gm.	gm.	gm.	
1	1200	...	1.4	34.	96	16	+62	...
4	3000	...	2.8	66.	134	16	+58	...
5	4440	...	3.6	142.	158	16	+16	...
9	4900	...	3.4	...	91	32	....	...
11	4740	23.	1.2	119.	70	24	—49	2.0
12	5520	...	..	166.	83	20	—83	...
13	3930	25.	1.4	157.	73	16	—84	...
14	3180	...	1.1	102.	48	16	—54	...
15	3330	27.	2.3	107.	38	16	—69	1.03
16	3510	...	2.4	133.	38	16	—95	...
17	3120	23.6	2.7	119.	35	16	—84	0.38
18	3180	22.	3.2	102.	30	20	—72	0.39
19	2400	17.	2.4	72.	50	20	—22	0.79
20	5280	...	3.3	116.	20	20	—96	2.56
21	2160	10.8	1.9	63.	44	..	—19	1.53
22	5910	25.8	3.7	100.	52	...	—48	7.93
23	5280	23.5	4.1	106.	17	8	—89	3.84
24	2400	17.3	3.1	77.	38	16	—39	3.48
27	2700	17.6	0.6	76.	50	12	—26	5.25
30	3360	...	2.3	54.	40	8	—14	...
62	1560	...	..	0.	69	0	+69	...

The absolute amount of ammonia rose slightly as the experiment advanced, but for this we have already given a partial explanation. On the twelfth day of the experiment (following the addition of 12 gm. of salt to the diet for three successive days) the amount of ammonia was greater than the quantity of ammonia obtained by Taylor on the last day of his experiment. Any lingering doubt as to the slight increase in ammonia obtained by Taylor on the last day of his experiment being dependent on the diminution of chlorin in the diet was thus dispelled.

While we were engaged in this work a patient with diabetes came under our observation, whose diet by chance contained an extremely small amount of salt. The case presented at first a mild form of diabetes with diffuse nephritis, but during a febrile attack the positive carbohydrate balance of 60 gm. changed to a minus carbohydrate balance of the most intense type. On the thirteenth day of observation the quantity of sugar in the urine was 157 gm., while the diet contained only 75 gm.

carbohydrates, thus giving a minus carbohydrate balance of 82 gm. This is about the maximum quantity of carbohydrates which could be formed out of the protein metabolized on this day, which was 25 gm. nitrogen (X 6¼) 156 gm. From this quantity of albumin it is customary to consider that (156 x 60) 94 gm. carbohydrate can be formed. Despite the severity of the case, the acidosis was only moderate, and on this day there was but 1.4 gm. ammonia.[6]

It is true that 16 gm. of sodium bicarbonate were administered in the twenty-four hours, but, as is well known, such a quantity will lower the ammonia only about 20 per cent. On the eleventh day of observation the chlorin in the urine was 2 gm.; on the fifteenth day, 1.03 gm.; on the seventeenth day, 0.38 gm., and on the eighteenth day, 0.39 gm. On the following day it began to rise as the low chlorin was discovered and salt was added to the diet. The observations made on this patient do not favor the view that a small quantity of salt in the diet of a diabetic patient increases the tendency to acidosis, because the general condition of the patient was better on the days with low chlorin excretion than in either the preceding or following periods, and the actual acidosis as measured by the excretion of ammonia was not notably affected. We would not attach too much significance, however, to this observation, because the excretion of chlorin may be variable even in the presence of a mild nephritis. The data of the case are recorded in Table 5. It is of interest that on the sixty-second day there was again a positive carbohydrate balance of 69 gm.

CONCLUSIONS.

The results of our experiments on two individuals placed on an ash-free diet for periods of thirteen and nine days, respectively, show no marked changes in metabolism. They simply represent the withdrawal of accessory salts from the body. They confirm the views of earlier writers, that it is practically impossible to diminish the chlorin of the body by more than 10 to 14 per cent., and that the loss of water is proportionate to this. No remarkable symptoms appeared, and those that

6. Such a severe case of diabetes with so slight an acidosis suggests a pancreatic origin as described by Brügsch (Therap. d. Gegenw., 1906, p. 337) and Hirschfeld (Berl. klin Wchnschr., 1905, xlii, 1609). No support for this opinion is furnished by the analysis of the feces which was made for me by Dr. F. B. Talbot: Total feces, 360 gm.; total dried feces, 20.758 gm. Percentage nitrogen, 4.2 per cent.; neutral fat, 1.9 per cent.; fatty acid, 3.9 per cent.; soap, 5.2 per cent.; total fat, 11 per cent. Total nitrogen in feces, 0.871 gm. Total fat in feces, 2.283 gm.

occurred were rather less than would be expected from such a diet, even though it contained a normal quantity of salts. We do not feel that they afford a basis for any far-reaching deductions as to changes in metabolism, and they certainly give no support to the view that the withdrawal of salts from the diet will cause an acidosis of the acetone variety. Clinical observations on the effect of the diminution of salt in a severe case of diabetes are in harmony with our experiments.

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THE INHIBITION OF PANCREATIC ACTIVITY BY EXTRACTS OF SUPRARENAL AND PITUITARY BODIES.*

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In a recent publication[1] we had the privilege of considering at some length the question of the activation of the pancreas by secretin, with especial reference to malnutrition and diabetes.

In it we pointed out, among other things, that in some animals, especially those which are carnivorous and are not provided with grinding molar teeth, in which animals there must, therefore, be either a large amount of acid gastric secretion or a high degree of acidity within the stomach, there was evidence that pro-secretin is present in the intestines in quantities larger than are found in human beings. We also reached the conclusion that the evidence to date for the absence or deficiency of pro-secretin as the cause of some cases of diabetes and malnutrition was insufficient.

These were our main findings as far as the present communication is concerned, but the experience gained in these connections led us to experiment further. The question of the relation of the pancreas and its evident activity, when excited by secretin, to digestion in general and to other organs in particular, is a very wide one, and, as we ventured to point out, offers a most promising and relatively unexplored field for research. It occurred to us that with a definite and sure method of activating at least the "external" secretion of that gland, and with an experience equal to measuring and interpreting its response, we had at hand a means whereby its correlation with other organs might be studied.

In his Harvey address[2] Starling says: "Secretin may be taken as a type of a whole group of chemical messengers, which, formed in one organ, travel in the blood stream to other organs of the body and effect

*From the Pepper Laboratory of Clinical Medicine, and the Laboratory of Experimental Surgery, University of Pennsylvania; reported before the Society of Normal and Pathological Physiology, University of Pennsylvania, March 30, 1908.

1. Sweet, J. E. and Pemberton, R.: The Archives Int. Med., 1908, i, 231.
2. Starling, E. H.: Jour. Am. Med. Assn., March 14, 1908, l, 835.

correlation between the activities of the organs of origin and the organs in which they exert their specific effect." This effect, he says, as a deduction from many observations in this connection, is not due necessarily to the formation of a special substance which shall exert a specific influence on some distant organ, but possibly to the development in that distant organ of a specific sensibility to the common product of the first organ. The chemical adaptations which Starling considers and of which we know most, have resulted almost exclusively in increasing the activity of the responding organ. "We can not, however, draw sharp lines between the reactions involving increased activity or dissimilation and those which involve increased assimilation or growth, since, under physiologic circumstances, the latter is always an immediate consequence or accompaniment of the former."

Some unknown function of the pancreas by virtue of which it seems to have a close relation with diabetes has long been recognized, chiefly from von Mering and Minkowski's well-known observation, that extirpation of the pancreas causes glycosuria. As is well known, many agents may cause glycosuria when injected intravenously or otherwise given; for example, isotonic salt solution injected intravenously in large amounts; interference with the supply of oxygen; etherization; and, lastly and more specifically, adrenalin injected subcutaneously. Whatever the mechanism by which these agents act the last one named does so by producing a true hyperglycemia. Now the fact, on the one hand, that a small excess of suprarenal substance in the circulation of an animal, its own suprarenal glands being intact, produces glycosuria, and, on the other hand, that extirpation of the pancreas produces a like result, suggests an antagonism or balance of action between these two organs in particular which might profitably bear investigation. A relation of this kind has been suspected, though full experimental evidence has been lacking to establish it. Thus, Herter has shown that painting the pancreas with adrenalin causes glycosuria, but whether this is merely a feature of its action when injected subcutaneously or intravenously is not yet known. G. Zuelser[3] has advanced some ideas as to the interrelation of the adrenals and the pancreas. To quote his own words, he makes "the assumption that the secretion of the suprarenals is normally neutralized by the pancreas and that, therefore, the 'pancreatic diabetes' of Minkowski, which follows extirpation of the pancreas, is really a suprarenal diabetes." He also claims that by injecting simultaneously

3. Zuelser, G.: Berl. klin. Wchnschr., 1907, xliv, 474.

suprarenal extract and pancreatic juice, no glycosuria results. Pflüger[4] has shown that extirpation of the duodenum in frogs causes glycosuria. (It is from the duodenum, of course, that the pancreas normally obtains the stimulus for the discharge of its external secretion at least.) Ehrman[5] has found that this extirpation does not cause glycosuria in dogs; but Pflüger criticizes Ehrman's work on the ground that the separation of the pancreas from the intestines was not complete and that the animals did not survive the operation for a period long enough to make the experiments conclusive.

It was, therefore, with the basal thoughts just suggested that we sought to investigate the influence of various factors on the one gland of the body whose excitation by "hormones" can be induced at will, as a basis for inquiring into that further interdependence of organs which we know exists. Our first thought was to look within the body for factors which might have some effect, though the question of outside influences, such as "drugs," is an important one of itself.

We attempted, therefore, at the start, to influence in dogs the flow of pancreatic juice when excited by secretin, with intravenous injections of adrenalin chlorid, taking 3 c.c. at a dose.[6] Three c.c. of adrenalin was sufficient instantly and markedly to increase the blood pressure, without evidently injuring the animal during the period of observation and in a few minutes the blood pressure fell again to normal, so that the dose could be several times repeated.

We found on injecting adrenalin chlorid that the flow of pancreatic juice was almost at once inhibited and in most cases absolutely so. With injection of fair amounts it was at all times slowed, proportionately to the size of the dog and the activity of his pancreas. Moreover, the simultaneous injection of secretin and adrenalin resulted in a total absence of flow; and, furthermore, the injection of adrenalin a few moments prior to the injection of secretin prevented a flow. Occasionally, if the gland were very active and the dose of adrenalin moderate, a slight response to

4. Pflüger: Arch. f. d. ges. Physiol., 1907, cxix, 227.

5. Ehrman: Arch. f. d. ges. Physiol., 1907, cxix, 295.

6. The secretin we used was prepared from normal dog intestines. The animals on which we experimented were all dogs. They were kept under profound ether anesthesia, and, at the end of the experiment, were killed. The amounts of secretin injected were 10 c.c. of solutions made from 300 to 400 c.c. 0.4 per cent. HCl. This quantity of acid was found well adapted to the extraction of mucosa from the upper four feet of dog intestines, and served for numerous observations, making a total of about 150 to 200 c.c. of secretin solution. The details of preparation are otherwise as given in our previous article (THE ARCHIVES INT. MED., 1908, i, 231).

flow would occur late, as though, in the end, the action of the secretory factor had preponderated.

In considering the matter, one of our first thoughts was, of course, that the inhibitory power of adrenalin was due to its blood-pressure-raising principle, notwithstanding the fact that changes in blood pressure are well known to have little influence in the output of most glands, and that the pressure in the secretory duct of such glands may, without much effect, be higher or lower than that in the vessels supplying it. This is well illustrated by numerous long-established experiments on the salivary glands. As a matter of fact, however, the injection of secretin is followed by an immediate and pronounced fall in the blood pressure. The blood-pressure-lowering element of secretin is probably purely incidental, as shown by Bayliss and Starling, and, as can be seen from our records, is a feature of many extracts of tissue because of various elements present. Further, under some circumstances, after the injection of adrenalin of known vasomotor activity, the blood pressure has for various reasons failed to rise very much, and again, after adrenalin injections, secretin has greatly reduced the blood pressure to a point much below normal, and yet no flow has resulted in either event, showing conclusively that this action is not the result of high blood pressure. Further, the simultaneous injection of both agents frequently results in such an antagonism of the elements which affect the blood pressure that no change in its level occurs and still no flow appears. We shall later refer fully, after considering further experiments, to some results obtained with old solutions of adrenalin which had undergone changes whereby they lost their property of preventing pancreatic flow, but yet powerfully raised the blood pressure. A flow, therefore, took place with the blood pressure raised almost to a maximum by adrenalin. More direct experiments to this end can be conducted with difficulty, as no other known substance raises the blood pressure to a degree at all comparable with adrenalin.

That this inhibition of secretion is not a feature of any general action of adrenalin is shown by a number of observations, the results of which are summarized as follows by Cushny:[7] "The secretion of the salivary gland and of the mucous glands of the mouth and throat is increased, apparently through stimulation of the nerve terminations, as under pilocarpin. The secretion is arrested by atropin, but can be reinstated by larger amounts of suprarenal extract, which is a more powerful antagonist to atropin than pilocarpin. The lacrimal gland and the bile

7. Cushing, Arthur R.: Pharmacology and Therapeutics, Lea Brothers & Co., Philadelphia.

are also increased." Speaking of the blood pressure, he says: "This active principle exists only in the medulla of the gland and, therefore, does not represent the whole function of the organ, in all probability."

It may be well here to mention the methods by which we recorded the observations which appear later. In our previous work we measured pancreatic activity by registering with a watch the exact moment at which the flow of juice through the canula in the duct of Wirsung passed definite graduations marked along the canula. This method was accurate enough, but not at all graphic and was, as well, voluminous in reproduction, so we had recourse to the following method:

The blood pressure was recorded on a kymographic drum by means of a manometer in the femoral or carotid artery, and the respiration by a manometer introduced into the trachea. By means of the electric push-button connected with the pen drawing the base line on the drum, it was possible, by watching the flow of juice through a graduated canula placed in the duct as usual, to record in vertical and momentary elevations of the base line the exact moments at which the juice flowed past any given division.

In order that the record of an experiment, which often covered a period of several hours, might be made continuous, we made use of a modification of the well-known "endless roll," a method which had for our purpose the advantages of recording the blood pressure in all its variations from the normal established at the beginning of the experiment.[8]

The experiments above recorded of the action of adrenalin were repeated a great many times and, as our tracings show, with almost invariably the same results. The amount generally used was 3 c.c. of the "adrenalin chlorid" of Parke, Davis & Co., which is said to contain two and one-quarter grains of chloretone to the ounce. In order to obviate the possibility of the latter preservative being a factor we prepared several chloretone solutions of different strengths, one of over twice the strength in which it occurs in adrenalin, but no inhibitory effect could be observed from it. We next made up a solution of pure adrenalin from the dried active extract of the suprarenal glands also on the market. This is said to contain no preservative of any sort, but a solution made from it of the same strength as that containing chloretone again gave the same results. Finally, we made a suprarenal extract of our own, from the suprarenal glands of thirteen dogs on which various surgical

8. We are under great obligations to Prof. E. T. Reichert for his kindness in devising the simple and effective kymograph which proved so perfect for the use of the endless paper roll. We are further indebted to him for assistance in many technical points.

operations had been performed some weeks previously in the course of experimental surgery at the University of Pennsylvania. These animals were in good health and were all killed by gas at the same time for autopsy study; advantage was taken of this fact to obtain the suprarenals. The glands were run through a hash machine and the resulting mass ground up with sand and about 30 c.c. of normal salt solution in a mortar for about fifteen minutes till the whole was reduced to a uniform pulp. Salt solution was then added to a total of 78 c.c. and the mortar contents strained through unbleached muslin. This preparation was opaque, white and cloudy in appearance, and our observations show that to all intents and purposes it had all the properties of that put on the market in regard to both blood pressure and inhibition of pancreatic flow. On an earlier occasion we made a normal salt solution extract from the two suprarenals of one dog and added to it 1 c.c. of a saturated solution of chloretone. This preparation was also active in all respects.

In order to establish any peculiarity or specificity of action in this connection, however, it was then necessary to utilize other glandular extracts and other substances in the same connection.

To this end we experimented with as many animal extracts of known activity as could be obtained. There are, of course, but few such, and there is only one of any definite therapeutic value, viz., the thyroid. A tablet of dried thyroid extract (the therapeutic dose for an adult human being) was ground up in a mortar and the powder rubbed up with 10 c.c. of water. The liquid assumed a brownish color, indicating some solubility of the substance, but for the greater part this injection consisted of a fine suspension. A solution of thyroid extract was also made by treating the mashed and ground pulp of two sheep thyroids with slightly more glycerin than was sufficient to cover them. This was allowed to extract all night and then diluted one-half with water, strained and used in various amounts for injection. There can be no question that this preparation contained much of the peculiar colloid thyroid elaboration, because the slightest amount gave the characteristic viscid reaction which occurs when the latter is treated with alkali. The glands used in this instance were taken from fresh material obtained from the abattoir and used at the University Hospital in the treatment of a case of myxedema which was improving rapidly. We also tried a liquid preparation of thyroid extract distributed by the manufacturers. All of the above thyroid extracts, however, were without influence on the flow of juice.

It has been shown by Schäffer and Oliver and others that the pituitary gland contains a substance which acts somewhat analogously to the active principle of the suprarenals, in that it raises blood pressure. It does this to a degree less than the latter, though the effect is said to be

continued somewhat longer. We attempted next, therefore, to obtain an extract of the pituitary body, and used first a liquid preparation said to be of the infundibular portion, distributed by Parke, Davis & Co. for experimental clinical observation. In answer to some questions addressed to them by letter, the manufacturers of this solution state that it contains 0.5 per cent. of chloretone. Taking the same dose of this that we used of adrenalin chlorid, we injected it after exciting the flow by secretin and obtained almost the same consequences as followed the use of adrenalin. In other words, the pancreatic flow was at once cut short and generally completely inhibited. In nearly every instance the rise in blood pressure was considerably less than is witnessed after the same dose of adrenalin, and, moreover, it was less abrupt, though the longer continuance noted by some observers was not so apparent. Notwithstanding its evidently inferior activity in respect to blood pressure, its inhibitory action on pancreatic juice seemed to be more marked. The cessation was in most cases more prompt, and on several occasions a second injection of secretin failed to excite a response after an interval of time following the injection of pituitary extract such as would probably have insured a flow, even though slight, had adrenalin been used, showing apparently that this preventive action sometimes lasts longer in the case of the pituitary gland. That this feature in no way depends on an increase in blood pressure is better illustrated by the pituitary than by the fresh adrenal extracts, since the former on many occasions fails to raise the blood pressure and more frequently the rise is so slight and so temporary as to be of evidently little consequence. In this respect of raising the blood pressure, the pituitary extracts used by us were by no means as constant or reliable as those made from the suprarenals.

On varying the time of injection, as we had done with adrenalin, and giving the extract after excitation of the pancreas by secretin, then before its excitation, and, finally, with the injection of secretin, we met with nearly identical results. In both of the latter instances the flow is prevented by the dose mentioned (3 c.c.), and in the former it is greatly slowed and generally promptly stopped. In regard to both the adrenal and pituitary extracts it is noticeable that their action is apparently more marked when the injections precede or are coincident with the injection of secretin than when they follow it. Sometimes, with a very active pancreas, the initial dose of adrenal or pituitary would be insufficient to retard very much a violent response to secretin, but we found that if given before the injection of secretin the flow was always inhibited.

The commercial extract of pituitary gland which we first tried (the exact nature of which was, of course, entirely unknown to us) was open

to the same theoretical objection as adrenalin, and it was possible that methods of preparation or the preservatives used in its manufacture might conceivably produce these effects or modify in some way its own properties; indeed, they might actually disguise those with which we were concerned. We, therefore, determined to prepare our own extract, which we did as follows:

On the occasion mentioned above, when thirteen dogs were killed, we removed separately both portions of the pituitary gland, nervous and glandular. This procedure is relatively simple in the dog, as the organ is easy of access and is exposed to view as soon as the frontal lobes of the brain are raised. The nervous part in the dog is a small white globule about the size of a grape-seed, and on being crushed extrudes a slightly viscid juice which can be rubbed into a paste. To the thirteen infundibular portions so treated we added 30 c.c. of normal salt solution, agitating the whole for some time to insure as complete extraction or solution as possible. The resulting fluid contained very little residue of any sort and was transferred directly to a small sterile Erlenmeyer flask. The glandular portion of the pituitary was then treated in the same way with an equal amount of salt solution and transferred to another flask. It might be mentioned here that, while histologically the glandular portion of the pituitary body is epithelial tissue, it in no way resembled a gland macroscopically, and by the uninitiated eye would be taken for the nervous element. On being crushed it resembles so much fairly dense tissue and gives a solution more tinged with blood than the nervous extract, which is almost white in color.

The extract from the nervous portion of the pituitary was active in regard both to blood pressure and to the suppression of the pancreatic flow, agreeing in all respects with the other preparations tried. The dose used was 10 c.c. of extract, which was equivalent to the nervous fraction of about four and one-third whole glands. The blood pressure was raised to a degree somewhat less than was seen after most of the other pituitary injections, but this may well be accounted for by the strength of the preparation, which must have been considerably lower in actual extractive content than the commercial article, which is made from the organs of larger animals.

The extract from the epithelial portion of the pituitary was injected without any evident effect on either the blood pressure or the flow of juice, which is quite remarkable, considering the immediate contiguity of the structures, and argues much for a specificity of action. We shall have more to say on this subject later.

Having satisfied ourselves that the pituitary and the suprarenal both contain something whose action on the pancreatic flow is marked, it remained now to investigate other tissues. The one of known physiologic interest as regards its therapeutic action we had already tried with a negative result, but it could not be postulated that other organs or other tissues might not contain some principle which would act analogously. Consequently we made extracts of the parenchyma of other glands and of other nervous tissue. Of the former the epithelial portion of the pituitary already served as a striking instance. About one-fourth of the liver of a freshly killed dog was put through a hash machine and then ground with sand and a small amount of normal salt solution in a mortar until a fairly uniform mass resulted. More normal salt solution was then added, making a total of 150 c.c. used, and the whole agitated and ground in a mortar as well as possible for about twenty minutes. It was then passed through unbleached muslin to free it from sand and tissue residue and then transferred to a sterile Erlenmeyer flask.

In addition to the above, on another occasion, a glycerin extract of liver was made by adding about 150 c.c. of glycerin to the mass passed through the hash machine as recorded, and after agitation and pressure in a mortar the whole was allowed to extract for twenty-four hours. A small amount of water was then added and the mass strained. Another watery extract had been previously prepared and this procedure was repeated only because it was thought that an unavoidable delay of some hours might in some way have impaired the activity of the first. With the exception just noted, the glandular extracts of our own preparation on which we based conclusions were all made within a few hours of the death of the dogs and injected within a few hours at latest after their preparation.[9] None of the liver preparations seemed, however, to have the slightest effect on the flow of juice, though the blood pressure was sometimes considerably lowered, as has been shown by Halliburton, Dixon and others to be the case with several organ extracts.

We next experimented with nervous tissue, for which purpose we obtained the brain of a freshly-killed dog, passed it entire through a hash machine and then ground the pulp in a mortar with sand and a total of about 130 c.c. aqua distillata. Distilled water was used inadvertently instead of normal salt solution, as in the other experiments.

While the subject of the depressing effect of extracts of nervous tissue has already been pretty thoroughly studied by Halliburton and others, it

9. The animals were killed between 6 and 7 a. m. The suprarenal and pituitary glands removed between 8 and 10 a. m., and extracts made by noon. They were injected during the afternoon and evening of the same day.

is interesting, apart from their relation to pancreatic activity, to compare the systemic effects produced by injections of this last preparation with those of other extracts. The amount of fresh liver substance taken for extractive purposes was about one-quarter of the organ, to which was added 150 c.c. of extracting fluid. The brain of a medium-sized dog compares closely with this in bulk as well as in percentage of water. We macerated the brain with 110 c.c. of extracting fluid, so that bulk for bulk the solutions were approximately equal, putting aside the question of their respective yields on attempts at extraction. The first dose of brain extract used was 10 c.c. and with a slight fluttering and preliminary rise of blood pressure the dog almost instantly died. The doses of liver and other tissue extracts were 10 c.c. and more. The next dose of brain extract was 5 c.c., and with a marked fall of blood pressure this animal died at once, though nothing had been previously injected into him. The next dose administered was 1 c.c. of extract in 10 c.c. H_2O, and again a fresh animal at once died; and finally we injected 0.25 c.c. diluted with 10 c.c. of water, and though the blood pressure fell alarmingly and it seemed by the cardiac inhibition and small excursion of pulse that this animal would also succumb, the blood pressure rose again and the animal seemed to recover. However, after one or two injections of secretin and adrenalin, which had been well borne in nearly every other instance, this dog also suddenly died, apparently from injury due to the first injection.

It is interesting to note that, notwithstanding the powerful and almost lethal effect of even a small dose of the watery extract of brain tissue, absolutely no effect could be detected on the flow of pancreatic juice, which continued, as we had frequently observed before, when the animal was moribund.

That the inhibitory action of the pituitary is therefore not a function of nervous tissue in general is clearly seen, because the mass of the brain as compared with that of the diminutive pituitary bodies is very great, and the effect of its extract, if potent, should be both actually and relatively greater. Moreover, the pituitary gland and brain substance are, of course, in the most intimate contact, and were this activity of the hypophysis common to other higher nervous tissue it is almost inconceivable that it should be so sharply differentiated in our work. Whether every part of the brain would act similarly in extract, or whether in such a gross method of extraction we have diluted, beyond evident potency, tissues from other active regions, is problematic.

In view of the relation which the pituitary is supposed to bear to the testes, as evidenced by those cases of acromegaly in which a lesion is dem-

onstrable in the hypophysis, and testicles also, it seemed advisable to try the effect of extracts from testicular tissues, although the immediate physiologic effect of these on the circulation and economy in general has been extensively studied by Dixon. We macerated two dog testes freed of their epididymes and then ground them up as before, with sand and mortar, finally adding a total of 78 c.c. of normal salt solution. The whole was then meshed through linen and injected in the usual manner, but no effect on the flow of juice was noticeable, whatever the time of the injections.

Our purpose in making glandular extracts of our own was two-fold. In the first place, such a procedure was necessary to give us the material we needed to widen the scope of our work; and, in the second place, it seemed advisable to test whether, by the methods we used, we could extract the features of certain glands which are known to be present in them. Failing in that, it could hardly be assumed that we were capable of extracting the active features of other parts; but if, on the other hand, we were successful, it could be reasonably believed that in the tissues under consideration no active substance was present, or that, if present, it was not susceptible of extraction by these methods. We desire to be understood, therefore, as claiming, not that this observed antagonism of action is one positively peculiar to two organs alone, but that it is one manifested by them under certain conditions of treatment and a property which we have been unable to extend as yet to other tissues. That a certain degree of specificity is probable from the evidence now at hand must be granted. Whether further observation will corroborate or disprove this it remains for the future to show.

We also experimented with atropin. According to the physiologists, atropin depresses or suppresses practically every secretory activity in the body except that of the kidney, and possibly the pancreas. On the flow of pancreatic juice, however, we were unable to perceive the slightest effect from it. The amounts administered were nearer the physiologic limit for a dog than were the doses of adrenalin, which can be repeatedly given in quantities of 10 c.c. at a time, in the form of the commercial adrenalin chlorid, without much evident injury. Our records show that one of our dogs received 1/300 gr. atropin sulphate, followed in a few minutes by another dose of 1/300 gr., without evident result on the flow, whereas another fresh dog died from what resembled paralysis of the respiratory center, apparently as the immediate result of an injection of 1/150 gr. Atropin neither prevented nor stopped the flow of juice.

Efforts were also made to simulate with digitalis the rise in blood pressure produced by adrenalin and pituitary extract, but no effect of any value could be obtained in this connection.

Now it is true that to speak of making an extract of so highly organized and differentiated a structure as the liver, not to mention the brain, seems crude; but it is also true that in considering such a problem as we have here we must first begin with the lowest terms and with such methods as are compatible with our knowledge of the subject. Having found in two organs some active substance which can be extracted by their treatment with salt solution, we are driven to applying the same methods to other parts of the economy if we would learn more of its extent and distribution. It can well be urged that in different sites the same property or different properties require different methods of extraction, and that treatment with water or glycerin in one instance will not effect the same result in another. Nevertheless, we have indubitable proof that both water and glycerin can extract certain of their activities from several organs, as, for example, the suprarenal and thyroid glands respectively, and we also have equal proof that from other regions of the body can be derived substances of such toxicity that an animal subjected to their action immediately succumbs. Just which of their numerous ingredients are responsible for these properties we are often unable accurately to say, and it is even a disputed point as to what factor in the extraction of nervous tissue produces the profound depression of the vascular system which is followed by death. That the same methods of attack, under such circumstances, should therefore necessarily appear superficial and crude follows perforce. When we consider how easy of extraction by almost identical means is that principle of the adrenals with which we are most familiar, namely, the blood-pressure-raising element, it seems astounding that its discovery should date from a period so recent as 1894; and if it be borne in mind that such methods in that instance furnished striking knowledge and that we have progressed little since then in our knowledge of the functions of the suprarenals themselves, the methods necessary in dealing with such an unknown subject appear less general and more definitely specific.

We hope to be able to investigate this antagonism of action, after separating the pancreas from its nerve supply, as thoroughly as possible, since it may well be that the effects noted result from the mediation of the sympathetic system. It is of some interest to consider here briefly a few points in the morphology of the suprarenals and the pituitary in their relation to our observations. It has been shown[2, 7, 10] that the

10. Dixon: Jour. Physiol., Cambridge, 1900-1901, xxvi.

classic effects of adrenalin are produced in large part by its action on the sympathetics, and wherever we test its action, in respects other than those under consideration, we find the results identical with those obtained by stimulation of this system of nerves and ganglia. The suprarenals are derived morphologically from two sources, the cortex coming from the mesoblastic tissue and the medulla from a direct outgrowth of the sympathetic system. As evidence of the latter we find in many of the lower orders distinct nervous tissues consisting of neurogliar cells, which are, however, harder to differentiate in man; indeed, in certain forms, viz., teleostean fishes,[2] the two parts, medulla and cortex, remain separate through life. Now, an interesting corollary to our observed analogy of action between the suprarenals and the pituitary is the fact that morphologically we could reasonably conceive of these two organs as having something in common. The pituitary body, like the suprarenals, consists of two parts, and again like the adrenals, each part has a separate derivation. The anterior lobe has its origin from one of the branchial clefts in a pouch of buccal mucous membrane.[11] The posterior is derived, like the medulla of the adrenal, from the ectoderm. It comes from the floor of the third ventricle, to which it remains attached by a stalk, viz., the infundibulum. According to some, the larger anterior lobe has two sources, the primitive oral tissue in early life and the anterior portion of the alimentary canal.[12] Wiederscheim[13] says that "the secretion from the pituitary gland formerly passed into the ventricles, and one of the more recent theories assumes that the pituitary corresponds to the primitive mouth (palæostoma) of the proto-vertebrata, which to a greater or less extent is represented by the combined impaired nasal and pituitary passage of cyclostomes." In certain mammals there can yet be seen evidences of the passage which connected the anterior part with the posterior part and thence with the third ventricle.[11] These facts by themselves are of interest, and in connection with our observations they are not in discord. That an organ so anatomically remote as the pituitary should have a definite influence on a gland in possible morphological relation to it is therefore less surprising.

As with the adrenals, it is that part derived from the nervous system which gives rise to the blood-pressure as well as the inhibitory element. For neither the epithelial portion of the pituitary nor the cortex of the suprarenals, however, is there any recognized function. The two parts

11. Herring: Jour. Physiol., Cambridge, xxxvi, No. 6.

12. Stengel: Text-Book of Pathology, Philadelphia, Saunders, 1906. Davidoff, Böhm: Text-Book of Histology, Huber, 1900, p. 380.

13. Wiederscheim: Comparative Anatomy of Vertebrates, Parker, 1897, p. 155

of the pituitary can be worked up and extracted separately, as noted above, but this has not yet been possible with the adrenal, so far as its inhibitory action is concerned, although from the suggestive analogies between these two organs and the very evident limitation of the inhibitory feature of the pituitary to its nervous moiety, it seems probable that the adrenalin inhibition has the same point of origin as the blood-pressure factor, viz., the medulla; still, this can not be postulated at present, and it may be, indeed, that we have here an expression of one of the functions of the suprarenal cortex.

Since the completion of our experiments some work has been reported by Botazzi, D'Errico and Jappeli,[14] in which they obtained an inhibition of flow from the salivary gland by painting it with adrenalin. Stimulation of the chorda tympani then failed to give a response. Without questioning the accuracy of their findings, which are at variance with the work quoted by Cushny, the question as they present it does not argue an inhibitory action on the salivary gland analogous to that observed by us on the pancreas. In the first place, they are dealing with a gland excited by purely nervous means and not by a chemical substance which reaches it through the blood. Again, and more important, the inhibited salivary gland is stated by the above Italian workers to be in the highest degree anemic after local application, a condition in which it is hard to conceive of its having an activity of any sort, since it is for the time being out of commission. This is, of course, in no way comparable to the action of adrenalin on the pancreas (if its action *is* on the pancreas) when the flow of juice in the latter organ is inhibited by a systemic injection into the jugular vein. And, furthermore, this view of the matter does not explain the action of the pituitary which has, as far as we know, no such reported action on glands. Finally, to ascribe to an ischemia of the pancreas the inhibition of pancreatic flow after jugular injection of a small dose of adrenalin, supposes that most or all of the organs of the body become anemic to such a degree that they can no longer act, which is stretching a hypothesis beyond the facts to support it.

It is somewhat immaterial, however, whether adrenalin acts on the pancreas alone or also on other organs, since the point of interest is that in affecting it at all in this way it affects the one gland of the body whose connection with diabetes is best established. That it might also affect certain other analogous structures with inhibition would not be surprising, though the evidence now is against it.

14. Botazzi, D'Errico and Jappeli: Physiol. Inst. Univ., Naples; Biochem. Ztschr., January, 1908, vii, 431.

One feature of our work demands some notice and is of suggestive interest. On the day when we experimented with the pituitary and suprarenal extracts of our own manufacture we made our first injections about 1 p. m. The preparations used for this purpose had been made between 10 a. m. and 12 m. from the animals killed early that morning as noted. The samples of suprarenal extract first injected were vigorously active. Because of press of work under the desire to utilize our preparations before they were affected by decomposition, we were unable to use the pituitary extracts before evening, about 8 p. m. Although tried then for the first time, about eight hours or more after their manufacture, they acted vigorously, as stated. On endeavoring to repeat with the suprarenal extracts our work with them of the early afternoon, however, we were able to get no inhibitory action, although the blood pressure was still raised. To control this conflicting observation we tried a preparation of adrenalin made some weeks previously from the dried extract of the suprarenal gland put on the market by Parke, Davis & Co. in small grain vials and said to be free from preservatives. This solution corresponded purposely, in adrenalin strength, to the usual commercial article containing the preservative chloretone. It was remarked by one of us immediately prior to the injection, while filling the syringe, that the solution showed a slight mould. It had been used many times before and had in every instance been powerfully and emphatically active, though there had been a lapse of perhaps a week since its last use. To our surprise, this preparation raised the blood pressure decidedly, but was absolutely without influence on the flow from the pancreas. We then tried an injection of the commercial adrenalin chlorid solution, also some weeks old but containing chloretone, which both raised the blood pressure and inhibited the flow, as we had repeatedly observed before.

The absolute significance of these observations can not be established until we repeat our experiments in this particular connection, but the most obvious and reasonable deduction is that the extracts from the suprarenal glands contain two or more substances, one of which acts on the blood pressure and one of which acts to inhibit the flow of juice. The former of these seems the more stable of the two and resists decomposition for a considerable time, but the latter loses its activity very shortly, perhaps in a few hours. In the instance of the preparations of our own manufacture, from dog organs, the tissues and the extracts from them were, of course, contaminated from the start with the ordinary postmortem putrefactive agents, and in order in no way to impair the efficiency of the extracts no attempt was made to introduce preservatives or sterilize them. The "dried extract" of the gland, however, was presumably

sterile to start with and the solution made from it remained fairly free from infection except in so far as it was contaminated by the initial weighing of the dry powder. Sterile salt solution was added to this and the solution kept on ice in a corked bottle, the only further contaminating agent, beyond contact with the air when the cork was removed, being the needle of the syringe. This was always thoroughly cleansed with water after each injection, though not sterilized. Under these circumstances decomposition would surely proceed rapidly from the start in the case of our dog preparations, but slowly in the case of the others. We can offer no explanation for the apparently greater stability of the pituitary inhibitory factor except that the pituitary glands, being small, were easily mashed in a small agate mortar and quickly transferred to small flasks, while the suprarenals required longer and more vigorous treatment with sand in a mortar, had also first been run through a hash machine, and were hence more open to infection.

The process which operated to destroy the activity of these preparations may be simply that of decomposition by putrefactive organisms, or it may be, on the other hand, of an oxidative nature more like that to which Bayliss and Starling have ascribed the slow deterioration of secretin and its more rapid loss of activity on evaporation in efforts to concentrate it. All the points here suggested are yet to be worked out, however, in their relation to our work.

We are by no means sure, at the present writing, of the full interpretation of the results under discussion. They are but the earliest steps in a line of work on which further observations may throw much light. They seem to us, however, to be very suggestive in their possible bearing on other interglandular relations, on the medium in which these are maintained, and possibly on a new conception of the interdependence of various organs now the subject of speculation. For these reasons it seemed advisable to publish our results at this stage and make their further amplification the subject of later contributions.

In studying the records, and indeed through a consideration of all our work, it must be borne in mind that we are dealing with a balance of power between various factors, no one of which is susceptible of exact definition or measurement. As with the study of the pharmacologic action of drugs, there must be taken into consideration, besides the size of the dose, the activity of the organ under consideration, and the condition and size of the animal as a whole. What may be quite sufficient markedly to affect one animal may be altogether inadequate in the treatment of another.

Popielski[15] has recently taken issue with Bayliss and Starling as to the method of action on the pancreas of acid extracts of the intestinal mucosa and indeed as to the existence of secretin at all, as a specific excitor. He also claims to be able to produce pancreatic activity with extracts of stomach and large intestine. The main point of discussion in this controversy is somewhat beside our present issue, though there are a number of incidental features which have a close relation to some observations of our own.

Popielski thinks that the secretion of pancreatic juice after excitation by secretin is dependent on a fall of blood pressure and that if the blood pressure be maintained high no flow results. He uses adrenalin to raise the blood pressure and notes with the high pressure that there is no flow. He concludes also, as an incidental point, that adrenalin, in itself, does not inhibit pancreatic activity. He considers that stimulation of the pancreas by secretin and stimulation by HCl in the duodenum are different processes. Now, it seems to us that our work throws some light on several of these questions. In the first place, we have obtained some further results with adrenalin (already mentioned and to be referred to again presently). Popielski's use of it seems to have been solely to raise the blood pressure. In so doing he has apparently overlooked the other feature of it, for, while he notes incidentally that it does stop the pancreatic flow, he thinks this phenomenon due to the high blood pressure and not to the adrenalin proper. He specifically states that adrenalin in itself does not influence the flow of juice. Now, as we mentioned above, one of our series of experiments conclusively proves that it is possible to obtain a flow after the injection of secretin, despite the fact that the blood pressure is raised to a high point. We refer to those observations, happened on by chance, in which exposure to air and apparent decomposition had destroyed the inhibitory factor of a solution of adrenalin, but allowed the blood pressure element still to act. Whatever the true explanation of this—and we offer nothing positive on this point—it is a fact that on several occasions such a solution distinctly raised the blood pressure sometimes to a very high point, and yet the juice flowed. To have noted this once would be sufficient to prove it possible. We have a number of such records. Not only does this prove that it is not the blood-pressure element alone of adrenalin which affects the flow of juice, but it also proves that, as just stated, a flow may take place following secretin when the pressure is high and that, therefore, a low blood pressure is *not*, as Popielski claims, a feature necessary to it.

15. Popielski: Arch. f. d. ges. Physiol., 1907, cxx, 451; 1908, cxxi, 239.

His findings in regard to the failure of atropin to affect the flow are in agreement with ours, viz., that no inhibition results from it. We have as yet been unable to effect a secretion from the pancreas by the injection of extracts of other tissues, though we have not yet tried those particular tissues (i. e., stomach and large intestine) used by Popielski. He states that a watery solution is sufficient to extract the exciting factor, and we used also water and normal salt solution in our work. We obtained no flow, but, on the contrary, from certain tissues, as mentioned above, we obtained an inhibition. We also made an acid extract of the pancreas with 0.4 per cent. HCl, and treated the whole exactly as we did a coincidently prepared and active solution of secretin. No flow resulted, however, from the acid extract of pancreas.

It should be mentioned also that after section of both vagi we still obtained the inhibitory effect from suprarenal and pituitary extracts.

Some further interesting observations have recently appeared which deserve reference. Fleig[16] reports on the physiologic properties and toxicity of normal pancreatic juice and that provoked artificially. He considers as normal, juice elaborated under the influence of chyme secreted through a duodenal fistula in an otherwise sound dog and then injected into the duodenum of the dog whose pancreas is under consideration. The quantities of chyme required under these circumstances are considerable (20 to 30 c.c.) and they must be repeatedly injected (every ten to twenty minutes) to induce a proper flow. The secretion thus provoked differs much from that which follows intraduodenal injections of 0.3 per cent. HCl, the time required is much greater and the quantity of juice furnished "infinitely less." Under the influence of chyme thus conducted the juice remains very thick and viscid from beginning to end, whereas juices secreted after more artificial stimulation differ in this and other physiologic respects until after repeated injections of secretin. For example, the pancreatic juice may have hardly any of its normal physical characters.

Natural and artificial secretions also vary in their toxicity when injected into animals, the former being more powerful in this respect. The lowered toxicity of secretin juices, Fleig thinks, is in consonance with their poor content of solids rather than their relative tryptic inactivity. He says that the above conditions are true also in general of the biliary and salivary secretions.

Now it seems to us that the above results are what might be expected. That a purely artificial and foreign substance, such as secretin, full of other extraneous matter and differing itself not only in quantity but in

16. Fleig: Compt. rend. Soc. de biol., May 8, 1905, No. 15.

quality from the normal pancreatic excitant, should produce the same juice as does the slow extruder gastric chyme, acting over perhaps many hours, seems unlikely in the highest degree. It would, indeed, be extraordinary if the results of such varied stimulation were the same. The amount of excitant which reaches the pancreas normally from the duodenum is surely a small or moderate quantity; that which is injected with secretin is not only concentrated in preparation from many feet of gut, but is injected in a few seconds to spend its whole force at once. It is hard to see how any gland could long continue to elaborate a normal product under such vigorous treatment. We hope to investigate shortly the effect of adrenalin and pituitary extracts on the pancreatic flow after stimuli other than secretin, especially chyme from a gastric fistula in an otherwise healthy dog, but it seems probable that the principles are much the same on which depends secretion after all of these and that the results of such work will be in harmony with what we have already seen. If adrenalin and pituitary extract inhibit the sudden and violent initial flow from secretin, it is conceivable that they would also affect the mild response from other stimuli. It must be remembered that the altered nature of pancreatic juice after secretin comes as the result of protracted and powerful stimulation and not from the initial dose.

It is interesting to note in connection with our work the observations of Meyer[17] and Frouin,[18] which afford some evidence that extirpation of the suprarenals, after the induction of diabetes in depancreated animals, modifies the severity of the diabetes and reduces the elimination of sugar.

We hope to concern ourselves now with the question of the site of this antagonism between the pituitary and suprarenal glands, on the one hand, and the pancreas, on the other; with the question of whether it is a chemical action, in the general sense of the word, which occurs in the circulation, or whether it is the result of some influence exerted on the pancreas alone; or whether, again, it is accomplished through a nervous mechanism. The solution of these problems should give information of value in studying the influence of such factors on the so-called "internal secretion" of the pancreas, and its relation to diabetes. Whether, on hypodermic injection, adrenalin produces glycosuria, which it does in a few minutes, by virtue of an inhibition of the internal secretion of the pancreas analogous to the inhibition of its external and visible discharge, is yet to be investigated. We have been unable to produce a glycosuria after either the subcutaneous or intravenous injection of 4 c.c. of pituitary extract. The solution used was made for us without

17. Meyer: Compt. rend. Soc. de biol., Feb. 14, 1908, p. 219.
18. Frouin: Compt. rend. Soc. de biol., Feb. 14, 1908, p. 216.

chloretone by the manufacturers, but we have not as yet controlled its inhibitory activity on the external pancreatic flow and, therefore, can not be positive on this point.

It yet remains to investigate more thoroughly the degree of specificity by trying the effects of other tissues and other methods of extraction; but, whatever the result of this, it appears reasonably certain that this feature to which we have called attention is one peculiar to certain structures, and from the data now available the expression of hitherto unknown properties of several organs.

In conclusion, it is a pleasure and a duty to express our great obligation to Dr. David L. Edsall for his constant and helpful interest in the work, and we also wish to thank Dr. John Marshall for many courtesies in the loan and equipment of apparatus.

CONCLUSIONS.

1. The suprarenal glands and the nervous moiety of the pituitary body in dogs contain something which, on extraction with salt solution and intravenous injection into dogs, cuts short the flow of pancreatic juice, after the administration of secretin. It also prevents the stimulation of the gland by secretin if its injection precedes the secretin.

2. This feature has been found, to date, in no other tissues.

3. It is independent of the general rise in blood pressure seen after the intravenous injection of adrenalin and pituitary extracts.

4. The inhibitory factor of extracts of the suprarenal glands seem to disappear by decomposition, oxidation, or other process, before the blood-pressure raising element is gone. It would appear that the suprarenal and the pituitary bodies have at least one property other than those qualities generally recognized as present in them.

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THE CLINICAL VALUE OF THE QUANTITATIVE ESTIMATION OF PEPSIN,

WITH SPECIAL REFERENCE TO THE METTE AND RICIN METHODS.*

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Beaumont's famous experiments showed that the gastric juice, even outside the body, had an active solvent action on food, and this led Müller to suspect the presence in it of a substance acting like diastase on starch flour. Eberle, in 1834, found this principle to be present in the acid gastric mucus. Müller and Schwann found that this was true of acid extracts of the mucous membrane, but that neither acid nor extract alone had any activity. Subsequent research showed that this was a property of the gastric mucus or secretion and not of mucus in general, as was originally surmised. Pepsin has since that time been exhaustively studied, and many remarkable facts have been demonstrated, the most interesting of which is Schütz's law, so-called, which is that the quantity of pepsin varies according to the square of the amount of albumin digested. In spite of all the effort that has been devoted to its study, pepsin, as such, has never been isolated in a pure state, so that it is impossible to estimate it quantitatively in a true sense of the word; all that can be done is to measure its effects and thus gain an idea of its concentration in a given solution.

The numerous quantitative methods for the estimation of the activity of pepsin have been so frequently reviewed that it is hardly necessary to discuss the older literature at length in the present paper. It will be sufficient to refer to the summaries in recent text-books, such as that of Boas, or to the articles of Koettlitz, Nirenstein and Schiff, Robin, Roth, and others. The following brief enumeration is, in part, after Roth:

1. The procedures of Bidder and Schmidt, Brücke, Gruenhagen, Jaworski, and Herzen are methods in which the stomach contents are diluted until no further digestion occurs or in which a certain amount of albumin or fibrin is exposed to the digestive action of pepsin for vary-

*From the Philadelphia Polyclinic and the Private Laboratory of Dr. John H. Musser. Read in the Section on Practice of Medicine of the American Medical Association, at the Fifty-ninth Annual Session, held at Chicago, June, 1908.

ing periods of time. The amount of pepsin is calculated with reference to the dilution required or the time elapsed. Grützner and Bourget used fibrin colored with carmin and estimated the amount of pepsin by the intensity of the red color of the gastric juice produced by the solution of the fibrin. Spriggs utilized the change in the viscosity produced by digestion as a measure of the ferment action. These methods at the best can only give approximate results.

2. Klug (Van Valzah and Nisbet) used the biuret test as a measure of the albumin digestion. The elder Schütz, Oppler and J. Schütz also calculated the amount of pepton formed; Schütz by the polarimetric method and Oppler and J. Schütz by the estimation of the total nitrogen. Oppler used the Kjeldahl method, but surrounded his test with so many precautions to secure natural conditions of ferment action and accuracy in results that it is generally regarded as the best and at the same time the least available of all methods.

3. In recent years Mette, Hammerschlag, Bettman and Schröder, Solms, Gross and others have introduced methods which aim at the exactness of the last-named procedure, combined with ease of application. Solms' test is described in full below. Bettman and Schröder determined the amount of pepsin by observing the rapidity with which the foam produced by shaking up an albumin solution containing pepsin is dissolved. Some of those who have employed this plan do not appear to have been favorably impressed (Cobb). Hammerschlag's method is too widely known to require detailed description. It is based on an estimation of the albumin in a special solution, before and after digestion, by means of the Esbach albuminometer. We have used it in a few cases and have found, as far as our limited experience goes, that the results correspond in a general way with those obtained by the Mette method.

The following table illustrates a few comparative tests with the Mette and Hammerschlag tests:

No.	Mette.	H.
M 498	4.3 mm.	97 per cent.
M 638	3.9 mm.	87 per cent.
M 505	3.2 mm.	81 per cent.

Hammerschlag's test is generally regarded as inferior to that of Mette and possesses many faults which have been enumerated by Roth and others.

The method of Mette, as modified by Nirenstein and Schiff, is generally conceded to compare in exactness with that of Oppler. The technic which we have employed is not widely different from that of Nirenstein and Schiff (cf. Sahli) and was described by one of us, with Dr. Sailer, a year or two ago. For the convenience of those to whom it is unfamiliar

it may be briefly described. Glass tubes, 1 to 2 mm. in caliber and 20 or 30 cm. in length, are filled by suction with white of egg, plugged with bread and boiled for five minutes. They are then sealed with sealing wax and after three days are ready for use. The test is carried out as follows: One c.c. of the gastric filtrate is diluted with 15 c.c. of N/20 hydrochloric acid. Two sections of tubing, 2 or 3 mm. in length, are added. A triangular file is sufficient for cutting the tubes. The specimen enclosed in a covered dish is kept in a thermostat at 37° C. for twenty-four hours. At the end of this period the column of albumin digested at each of the four exposed ends is carefully measured in tenths of a millimeter. An average of the four readings is recorded as the result, but it is usual to square this for comparison with other tests in accordance with Schütz's law.

The following examples will make this clear:

No.	Dil.	Reading.	Squares.	Relative Strength.
P.271	1 in 4	6.8	46	4
P.271	1 in 16	3.4	11.6	1
P.273	1 in 4	6.4	41	4 (approx.)
P.273	1 in 16	3.3	10.9	1

Mette's test thus modified excludes various errors which impair the value of many other methods, because it possesses the following advantages:

1. The acidity in all cases is rendered approximately uniform without any tedious titrations being required.

2. The dilution is sufficient to overcome inhibition due to albumoses (Sailer and Farr), etc., or antiferments.

3. A uniform surface is exposed to digestion at all times.

4. Numerous observations show that it complies with Schütz's law in dilutions sufficient to avoid inhibition and to prevent a digestion of more than 4 mm.

Objections to the method are:

1. Albumin from different eggs or albumin coagulated at different temperatures or heated for different periods of time varies considerably in digestibility.

2. Differences in the caliber of the tubes beyond certain limits affect the readings.

3. Wide variations in the temperature of the thermostat have the same effect.

4. There is a decided personal index in measuring the column of albumin.

These faults can be largely overcome by the following measures:

1. An unvarying technic and the use, possibly, of artificial or dried egg albumin of uniform quality (Onuf).

2. The use of an artificial pepsin control. For this purpose a 1 or 2 per cent. solution of a standard pepsin should be employed, diluted 1 in 16 in the same way as the specimens to be examined.

3. A uniform method of measurement.

In these tests we employed an ordinary clinical microscope (low power) fitted with a movable stage and vernier scale.

Two illustrations will show the value of controls where there are wide discrepancies:

(a) No.	Mette.	(b) No.	Mette.
M 273	5.2	M 511	4.4
M 282	5.8	M 520	2.8
M 251	2.8	M 638	3.9
Control pepsin, 1/16 per cent.	4.2	Control pepsin, 1-16 per cent.	2.8

Comparison in these cases leads us to lay less stress on the high figures obtained in the first experiment. Similarly M. 251 can be regarded as a case of greatly diminished pepsin, while M. 520 with the same reading is merely a low normal.

Jacoby, in 1906, in a short article disputing Pawlow's assertion that pepsin and rennin were identical, introduced a new method of determining pepsin, which, he claims, decided definitely the individuality of the two ferments. This method was by means of ricin, a solution of which, he found, was cleared up by pepsin. Although this peculiar property had been observed by him some time before while pursuing his study of ricin, its adaptability to clinical use was not brought forward until Solms published his paper in 1907.

Jacoby had found that, if pepsin were added to a 1 per cent. solution of ricin in salt solution, the cloudiness due to the albuminous substances in the ricin disappeared rapidly and completely. Working on this under Jacoby's direction, Solms evolved the following simple procedure, the only fluids needed being a solution of ricin and a N/10 hydrochloric acid solution:

The ricin solution is made by dissolving 0.5 gram of ricin in 50 c.c. of a 5 per cent. sodium chlorid solution and filtering. (The recin used by Solms was obtained from the Vereinigte chemische Werke, Charlottenburg, Salzufer 16, costing 2 marks for 10 grams. Solms preferred this preparation of ricin to Merck's, principally on account of the limited supply and the great cost of the latter.) The filtered ricin solution has a somewhat cloudy appearance, but on the addition of 0.5 c.c. N/10 hydrochloric acid solution becomes decidedly milky. The milky appearance is cleared up by pepsin.

His technic is as follows: The gastric juice is obtained by extracting the stomach contents one hour after the ingestion of an Ewald-Boas test breakfast. He tests this for the presence of free hydrochloric acid, then determines the total acidity, and in appropriate cases examines for lactic acid. According to his findings he makes varying dilutions of the contents with distilled water. In cases of hyperacidity he dilutes the filtered contents from 1:100 to 1:10000, whereas in cases of anacidity or subacidity the dilutions vary from 1:10 to 1:100. In normal cases he dilutes from 1:100 to 1:1000.

In each of the five test tubes he puts 2 c.c. of the filtered ricin solution; then with another graduated pipette he adds 0.5 c.c. N/10 hydrochloric acid, which causes the mixture to become very cloudy. Having numbered the test tubes 1, 2, 3, 4 and 5, he puts in the first tube 1 c.c. of boiled gastric juice; in the second, 0.9 c.c.; in the third, 0.8 c.c.; in the fourth, 0.5 c.c., and in the fifth, 0 c.c. Then he takes the unboiled juice and, having diluted 1 c.c. of juice with 99 c.c. of water, he puts in the first test tube 0 c.c.; in the second, 0.1 c.c.; in the third, 0.2 c.c.; in the fourth, 0.5 c.c., and in the fifth, 1 c.c., so that in each tube there are 3.5 c.c. of fluid. The test tubes are then corked and put in an incubator, where they are allowed to stand for three hours; at the end of this time they are taken out and the tubes examined to see with what dilution the ricin has been cleared up. If an incubator is not at hand the tubes can be left at room temperature, of course for a correspondingly longer time.

In order to obtain a convenient expression of the pepsin content of a gastric juice, he designates that amount of pepsin contained in 1 c.c. of a 1:100 dilution, which is capable of clearing up the ricin solution after three hours' standing in an incubator, as 100 pepsin units. This he has decided on as the normal standard, because after many examinations of specimens of normal acidity he found the ricin to be cleared up by 1 c.c. of a solution diluted 1:100. Solms considers the normal acidity to be 40 to 60, and anything above or below this to be hyperacidity or hypoacidity, and gives tables showing the pepsin content in these various conditions. His tables show no fixed relation between the acidity and the amount of pepsin, except in those cases in which the acidity is very low or the free hydrochloric acid entirely absent, under which conditions the pepsin will be found to be low also. Solms thinks that from a study of his tables he has learned nothing which would tend to show that the estimation of pepsin has a diagnostic or therapeutic value.

Witte studied this new method of Jacoby and Solms and recommends it strongly on acount of its simplicity and cheapness. The only modification he proposes is to add a dilution of 1:50, since in his experience

there have been cases where a dilution of 1 : 100 did not quite dissolve the ricin. His conclusions are about the same as those of Solms, namely, that the normal pepsin unit is between 100 and 200 and that there is but slight relation between the acidity and the amount of pepsin, except in cases of lowered acidity, in which the pepsin is likely to be lower. Witte made a few comparisons with the Mette method, but prefers the ricin procedure.

TABLE 1.—NORMAL ACIDITY—40-60.

Serial No.	Total Acid.	Free Hcl.	Ricin.	Mette.	Diagnosis.	Case No.
1	40	0	100 not clear.	1.6 (2.6)	Carcinoma pylorus.*	F. S.
2	40	30	100-200	3.8 (14.4)	Hyperchlorhydria	M., 464
3	42	+	100	3.1 (9.6)	Chr. constipation	P., 335
4	43	+	Not made.	3 3 (10.9)	Hyperchlorhydria	P., 273
5	44	26	200	3 2 (10.2)	Gastro-enteroptosis	M., 365
6	48	10	100	4.9 (24)	Chloro-anemia	M., 311
7	50	18	10	3.9 (15.2)	Chr. gastritis	M., 570
8	50	30	200	4.4 (19.4)	Migraine—dilatation of stomach	M., 511
9	50	+	100 not clear.	0.5 (0.25)	Pyloric obstruction†	G. C.
10	50	+	Not made.	3.2 (10.2)	Constipation—nervous dyspepsia	P., 300
11	50	+	Not made.	4.9 (24.0)	Chr. constipation	F. B.
12	54	34	100-200	4.3 (18.5)	Gastric neurosis	M., 434
13	54	36	100	Not made.	Tubercular enteritis	M., 659
14	56	24	100	Not made.	Cholecystitis	M., 884
15	58	30	100 not clear.	3.7 (13.7)	Hyperchlorhydria	M., 402
16	58	34	100	3.0 (9.0)	Neurasthenia—gastric neurosis	M., 449
17	60	45	100	5 2 (27.0)	Cholecystitis—hyperchlorhydria	M., 791
18	60	+	100	5.0 (25.0)	Malnutrition—chr. pancreatitis(?)	S. C.
19	45	20	100	Not made.	Gastric neurosis	M., 653

* Without preliminary lavage. Lactic ac. +. Lower dilution of ricin not made.
† Probable carcinoma. Butyric acid. Lower dilution of ricin not made.

Gross advances a new method which he claims to be simpler than the foregoing. His method is based on the precipitation of undigested casein by sodium acetate, but we have had no opportunity of studying its value. Gross claims that the Jacoby-Solms method is open to criticism on one point, and that is that the ricin they used is very impure and that there is no way of determining just what foreign bodies are mixed with it. He also objects to the method on grounds of expense, but this, depending merely on a personal point of view, requires no comment.

In making our studies we have followed closely the technic as laid down by Solms and have seen no reason to make any change or modification. The only drawback we have encountered is that the ricin solution must be freshly prepared. We tried making up a large amount, and filtering it only as needed, but the filtrate was so cloudy that it was difficult to determine the extent of pepsin digestion, as the solution did not become clear even when the gastric juice was but little diluted. After the ricin solution is once made, the preparation of the five tubes for peptic digestion occupies very little time, not more than seven minutes on an average, when once the technic has been perfected.

The results of our studies are shown in the accompanying tables, which are self-explanatory.

SUMMARY OF THE TABLE OF NORMAL ACIDITY (40-60).

Apart from three cases, Nos. 1, 9 and 18, the ricin and the Mette methods gave results within normal limits. In our table the ricin results of Case 1 is reported as "100 not clear," but in this case, as in Case 9, lower dilutions than 1:100 were not made. Finding that 100 was not digested, we should have begun with a dilution of 1:10, when there would doubtless have been a low reading corresponding with that by the Mette method. Case 18 shows the Mette result to be at the extreme upper limit of the normal, while the ricin remains exactly normal. From a study of the table we see that, apart from those cases with organic acids or diminished free hydrochloric acid, no aid in diagnosis other than that derived from the ordinary chemical examination has been obtained by the determination of pepsin. In Case 9 retention, favoring the production of organic acids, is the cause of the relatively high acidity. The same case (Table 2, 10), after lavage, showed a very low acidity and a minimal amount of pepsin. Therapeutically, the table is suggestive, but nothing more.

SUMMARY OF THE TABLE OF LOW ACIDITY (BELOW 40).

With low acidity the pepsin is also low, both by the ricin and Mette methods. In two instances, Cases 8 and 5, the Mette was normal, while the ricin was absent or diminished, respectively. This discrepancy can be explained, as the controls for the Mette tests were also high. In Case 14 the ricin was normal, while the Mette was subnormal. We have no explanation to offer for this variation.

Pepsin determination seems to be of value in distinguishing simple gastritis and neuroses from achylia and carcinoma. In the last two the

pepsin is invariably very much diminished, whereas in the first two it is unaffected or but slightly altered. In this we disagree with Witte, who found that pepsin was always low in neuroses.

SUMMARY OF THE TABLE OF HYPERACIDITY (ABOVE 60).

With very few exceptions, the ricin and the Mette methods coincided in cases of hyperacidity, although the former is not capable of showing the finer gradations of the latter. In two cases, 27 and 55,

TABLE 2.—SUBNORMAL ACIDITY—BELOW 40.

Serial No.	Total Acid.	Free Hcl.	Ricin.	Mette.	Diagnosis.	Case No.
1	35	0	10-20	2.3 (5.3)	Endarteritis—chr. tuberculosis. . .	M., 140.
2	34	+	Not made.	3.4 (11.6)	Constipation—Subacidity.	P., 271.
3	28	6	10	2.8 (7.8)	Cholelithiasis—gastritis	M., 251.
4	26	0	20-50	2.0 (4.0)	Polycythemia—chr. gastritis*	M., 814.
5	26	8	10-20	3.3 (10.9)	Gastric neurosis	M., 579.
6	25	0	10	0.8 (0.64)	Pyelitis	M., 189.
7	22	0	10	1.0 (1.0)	Chr. gastroenteritis†	M., 813.
8	22	0	0	3.4 (11.6)	Chr. gastritis	M., 571.
9	20	0	0	0.1 (0.1)	Anacidity	M., 576.
10	12	0	Not made.	0.5 (0.25)	Carcinoma pylorus‡	F. S.
11	12	0	Not made.	0.8 (0.64)	Chr. Diarrhea—achylia gastrica§. .	P., 350.
12	12	0	Not made.	0.5 (0.25)	Incipient tbc.—splanchnoptosis	P., 15.
13	4	0	Not made.	0	Achylia gastrica achylia gastrica	P., 270.
14	18 (1)	+	100-200	2.4 (5.7)	Spastic stricture of esophagus. . . .	P., 302
15	34 (2)	+	100 not clear.	2.2 (4.8)	ib**	ib.
16	6 (3)	0	10 not clear.	0	ib††	ib.

* Vomitus.
† Lactic acid present.
‡ Lactic acid present after lavage. See F. S., Table 1.
§ No lactic acid.
|| Lactic acid present.
** Lower dilution of ricin not made.
†† Contents of esophageal dilatation.

the ricin was 1,000, while the Mette was also high. In Case 37 there was a disproportion between the two methods, the ricin being 1,000 while the Mette showed a normal value. In this case two dilutions of ricin were made, one of 1:100 and the other 1:1000, in each of which the result was 1,000 units. In two other cases, 53 and 56, the ricin was abnormally high and the Mette low, which can be explained by the low result obtained in the control experiment.

Here our efforts to find some diagnostic aid in the quantitative estimation of pepsin have met with failure. The fact that there is no definite relation between the degree of acidity and the amount of pepsin might suggest the use of artificial pepsin in occasional cases.

COMPLETE SUMMARY.

Our tests indicate that the normal variation of the Mette method is between 3 (9) and 5 (25), of the ricin method 100 to 200. In carcinoma ventriculi, achylia and occasionally in chronic gastritis, the pepsin determination reveals values below the minimal normal, but as a rule in neuroses and chronic gastritis the pepsin is relatively but little affected in contradistinction to carcinoma and achylia, and this would seem to be of assistance in making a differential diagnosis between these conditions. We have found, as have others, that within normal limits there are wide variations without apparent relation to the acidity, but at present we are not in a position to draw any diagnostic or therapeutic conclusions from these observations.

The results obtained with the ricin method correspond with those shown by the Mette method; that is, normal values and subnormal values are clearly shown, but the finer variations are not seen and when present frequently do not correspond with the Mette results. This is true even when we have made allowance for differences in the Mette tubes by means of the controls referred to above.

Both tests are valuable as rough quantitative methods, and they are carried out with equal facility. The Mette has the advantage of excluding variations due to differences in acidity without requiring any previous titration. There has been no attempt made to see whether the ricin method follows the law of Schütz, nor has there been any attempt made to bring the various tubes to a uniform acidity. The variation in the acidity of the five tubes would seem *a priori* to be fruitful of grave errors. This could probably be obviated by suitable dilutions with N/20 hydrochloric acid, similar to those employed by Nirenstein and Schiff in their modification of the Mette method. These questions may form the basis of a supplementary communication.

We have made little therapeutic use of the knowledge we have obtained. The wide variations in the pepsin values would suggest that the drug has been too much despised by stomach specialists, though this can not be said of practitioners in general. It would seem to be indicated in cases showing subnormal peptic values, with preservation of at least a fair degree of acidity. In chronic gastritis with low acidity and low pepsin, in achylia and in carcinoma it would be necessary to add hydro-

TABLE 3.—HYPERACIDITY—ABOVE 60.

Serial No.	Total Acid.	Free Hcl.	Ricin.	Mette.	Diagnosis.	Case No.
1	62	+	Not made.	3.2 (10.2)	Gastric ulcer.	P., 310
2	62	+	Not made.	3.8 (14.0)	Constipation—chronic gastritis.	P., 229
3	62	+	100	4.6 (21.2)	Cholelithiasis—pyloric adhesions.	P., 289
4	62	30	100-200	Not made.	Goiter—dilated stomach	M., 871
5	62	34	100	2.8 (7.8)	Psoriasis—eczema.	M., 520
6	62	36	100-200	4.1 (16.8)	Gastric neurosis.	M., 300
7	62	16	10	3.8 (14.4)	Carcinoma pylorus*	M., 227
8	64	40	100	3.3 (10.9)	Neurosis.	M., 575
9	64	30	100	Not made.	Nephritis—gastritis.	M., 824
10	64	48	100	3.1 (9.6)	Adhesions(?)—hyperchlorhydria	M., 615
11	64	+	Not made.	2.3 (5.3)	Chronic gastro-enteritis.	P., 272
12	65	40	100-200	3.6 (13.0)	Glycosuria.	M., 500
13	65	40	100	3.4 (11.6)	Syphilis—neurasthenia.	M., 176
14	66	40	100	2.8 (7.8)	Myalgia	M., 680
15	66	36	100	3.2 (10.2)	Tachycardia.	M., 236
16	66	40	100	Not made.	Gastroptosis—gastric neurosis	M., 225
17	67	+	Not made.	3.4 (11.6)	Epilepsy.	P., 324
18	68	24	200	3.6 (13.0)	Frontal sinusitis—neurosis—hyperacid.	M., 423
19	68	42	200	4.3 (18.5)	Gout—neurosis—alcoholic gastritis.†	M., 498
20	68	34	100 not clear.	3.3 (10.9)	Pancreatitis—hyperchlorhydria.	M., 356
21	68	46	100-200	4.6 (21.2)	Cholecystitis—gastric ulcer.	M., 322
22	68	+	100	4.0 (16.0)	Hypochondriasis.	F. W.
23	68	+	Not made.	3.2 (10.2)	Gastric ulcer.	F. M.
24	68	44	100-200	5.9 (34.8)	Chr. appendicitis—gastric neurosis.	M., 757
25	70	40	100	Not made.	Jaundice—cholecystitis.	M., 664
26	70	40	100-200	4.0 (16.0)	Gastritis—hyperchlorhydria.	M., 734
27	70	54	1000	5.8 (33.6)	Hour-glass contraction of stomach—pyloric adhesions.	M., 282
28	70	46	100	3.2 (10.2)	Fibroid of uterus—hyperchlorhydria	M., 371
29	73	+	Not made.	4.4 (19.4)	Constipation—hyperchlorhydria.	P., 258
30	74	44	100	4.7 (22.0)	Hyperchlorhydria—pylorospasm—cholecytitis—chr. appendicitis.	M., 335
31	75	55	100	3.0 (9.0)	Hyperchlorhydria.	M., 538
32	75	40	100-200	3.0 (9.0)	Exophthalmic goiter	M., 455
33	76	30	100	4.0 (16.0)	Appendicitis.	M., 326
34	76	+	Not made.	3.0 (9.0)	Splanchnoptosis.	S P.
35	76	+	Not made.	5.4 (29.1)	Gastroptosis—hyperchlorhydria.	P., 193

* Vomitus.

† Hammerschlag, 97%.

TABLE 3.—CONTINUED.

Serial No.	Total Acid.	Free Hcl.	Ricin.	Mette.	Diagnosis.	Case No.
36	78	56	100	3.5 (12.3)	Chr. appendicitis	M., 593
37	78	64	1000	3.8 (14.4)	Appendicitis—hyperchlorhydria.‡	M., 476
38	78	36	100	3.9 (15.2)	Hyperchlorhydria	M., 450
39	78	40	100	3.8 (14.4)	Gastric ulcer	M., 430
40	80	+	Not made.	4.0 (16.0)	Splanchnoptosis—incipient tbc	P., 296
41	80	55	100	3.4 (11.6)	Hyperchlorhydria	M., 678
42	80	55	100	3.0 (9.0)	Hyperchlorhydria	M., 585
43	82	52	100	3.0 (9.0)	Hyperchlorhydria	T. T. M.
44	82	32	100	3.8 (14.4)	Bronchitis—gastritis	M., 599
45	82	+	100	4.6 (21.2)	Cholelithiasis—hyperchlorhydria	F. B.
46	82	54	100	3.4 (11.6)	Gastritis	M., 689
47	84	52	100	3.1 (9.6)	Hyperchlorhydria	T. M. B.
48	84	60	100	Not made.	Neurosis—hyperchlorhydria	M., 883
49	85	35	100	2.9 (8.4)	Neurasthenia—gastroptosis	M., 602
50	85	55	100	2.6 (6.8)	Gastric neurosis	M., 667
51	86	48	100	4.9 (24.0)	Gastric neurosis	M., 561
52	86	58	100	5.2 (27.0)	Appendicitis—hyperchlorhydria	M., 273
53	88	54	500	2.8 (7.8)	Cholecystitis—hyperchlorhydria.§	M., 171
54	88	58	100-200	4.9 (24.0)	Frontal and ethmoidal sinusitis—hyperacidity.	M., 785
55	88	62	1000	5.3 (28.0)	Gastritis—hyperchlorhydria?	M., 334
56	95	60	500	3.1 (9.6)	Neurosis—hyperchlorhydria	M., 489
57	100	45	100	2.9 (8.4)	Gastric ulcer	M., 597
58	106	94	100-200	Not made.	Cystitis—enteritis	M., 828
59	110	62	200	3.7 (13.7)	Epilepsy(?)	M., 713
60	112	+	Not made.	4.2 (17.6)	Hyperchlorhydria	P., 341

‡ Two controls, first with dil. of 1:100; second with dil. of 1:1000.
§ Mette control also low.

chloric acid. In many cases it is doubtful if enough acid could be introduced, except occasionally with a stomach tube, to allow of normal proteolysis. A practical expedient (Sailer) is to saturate meat or milk, before taking, with dilute hydrochloric acid until free acid can be detected, after which a small dose of hydrochloric acid will suffice. Pepsin should be given in sufficient amounts to make a 1/4 to 1/16 per cent. solution in the contents of the stomach (estimated in advance). It should be given with or followed by at least twenty minims of dilute hydrochloric acid. Both may be repeated once or twice at short intervals to make up

for the amount expelled into the duodenum. Gasterine, or the normal gastric secretion of the dog obtained through a Pawlow fistula, has been advocated by Frémont and others (see Bettmann) in doses of 100 to 500 c.c. We have had no experience with it, but it would seem to have no advantage over a mixture of pepsin and hydrochloric acid unless it possesses some "vital" or other property independent of its principal constituents.

In conclusion, we desire to acknowledge our indebtness to Drs. Musser, Sailer and Talley for the use of their clinical material, which we have freely used to supplement our own.

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